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Vaso Butozan (Starčevo, RS, 5 December 1902 – Zagreb, HR, 14 May 1974) graduated from the Faculty of Veterinary Medicine, University of Zagreb, in 1930. Immediately after graduation, he was appointed assistant at the Department of Histology and Embryology, Faculty of Veterinary Medicine, Zagreb. He received his doctorate from the same faculty on 30 June 1931. He participated in the National Liberation War from 1941. From 1949 to 1950, he served as the first rector of the University of Sarajevo. He was elected a full member of the Scientific Society of Bosnia and Herzegovina in the Department of Medical Sciences in 1952. He was president of the Scientific Society of Bosnia and Herzegovina (1959–1966) and the first president of the Academy of Sciences and Arts of Bosnia and Herzegovina (1966–1968).

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Treatment Stability of Warfarin and Acenocoumarol in Patients With Mechanical Heart Valves and Atrial Fibrillation: A One-Year Cohort Study

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Abstract

Objective. This study aimed to investigate which of the two vitamin K antagonists, warfarin or acenocoumarol, provides more stable anticoagulation control in patients with mechanical heart valves and atrial fibrillation. **Patients and Methods.** This was a prospective, one-year clinical cohort study. In total, 73 outpatients with mechanical heart valves and atrial fibrillation who were already treated with warfarin or acenocoumarol were recruited from the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina. The prothrombin time target values, expressed as the international normalized ratio (INR), were 2.0–3.0/4.0. Numerical data between the treatment groups were summarized descriptively. **Results.** Patients in the warfarin (N=35) and acenocoumarol (N=38) treatment groups were similar in terms of sex, age, body mass index, body surface area, and number of concomitant drugs known to interact with vitamin K antagonists. The number of INR measurements per patient, number of INR measurements within the therapeutic range per patient, mean time interval between successive INR measurements, and mean INR values across consecutive measurements were similar in both groups. However, compared to acenocoumarol, warfarin treatment seemed to be associated with more stable anticoagulation, i.e., with a higher mean time in the therapeutic range (TTR) (76.1±24.2 vs. 69.1±21.5%) and a smaller proportion of patients below all predefined TTR thresholds (<60%, <65%, and <70%). **Conclusion.** Our unadjusted descriptive results suggested that warfarin, compared to acenocoumarol, may provide more stable and therefore safer anticoagulation control in patients with mechanical heart valves and atrial fibrillation. To confirm this, larger prospective clinical studies are needed in patients with mechanical heart valves with or without atrial fibrillation.

Key Words: Mechanical Heart Valves ▪ Atrial Fibrillation ▪ Warfarin ▪ Acenocoumarol ▪ INR ▪ Treatment Stability.

Introduction

Although new oral anticoagulants are available, the vitamin K antagonists (VKAs) warfarin and acenocoumarol remain irreplaceable for lifelong prevention and treatment of thromboembolic complications in patients with mechanical heart valves (1, 2). Given the narrow therapeutic index of VKA therapy, which presents risks of thromboembolic complications on one hand and bleeding on the other, the physician's primary goal is to maintain it within optimal and stable anticoagulation control. To achieve and maintain optimal anticoagulation treatment, the American College of Cardiology (ACC) recommends targeting international normalized ratio (INR) values of 2.0–3.0 for patients with low-risk aortic valve replacement (AVR) and INR values of 2.5–3.5 for patients with high-risk AVR and mitral valve replacement (1). According to the European Society of Cardiology (ESC) and the European Association

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for Cardio-Thoracic Surgery (EACTS) the target INR should be adapted to each patient's prosthesis thrombogenicity and individual risk factors, i.e. for valves with low thrombogenicity the target INR is 2.5 (without risk factors) or 3.0 (with ≥1 risk factor), for medium thrombogenicity INR is 3.0 or 3.5, and for high thrombogenicity, INR is 3.5 or 4.0 (3).

A time in therapeutic range (TTR) of ≥65% is commonly accepted as the definition of INR stability (4). For patients with stable INR values, previous recommendations suggested monitoring every four to eight weeks, and current guidelines allow extending this interval up to twelve weeks (4, 5).

Due to the differences in pharmacokinetics (PK), i.e., the longer elimination half-life attributed to warfarin (20–60 vs. 8–10 hours), warfarin anticoagulation treatment is considered more stable compared to acenocoumarol (6). In addition to PK, patient age and body weight, and regardless of indication, genetic factors largely determine the anticoagulant effect and, therefore, the dose of VKAs in patients with mechanical heart valve replacement (7). Gene polymorphisms are important factors responsible for variability in warfarin dose requirements (8). According to a recent study, one-third of all variations in response to warfarin are the result of mutations in two genes: a gene for cytochrome P450 (CYP2C9) and a vitamin K-epoxide reductase gene (VKORC1) (9). The PK and pharmacodynamics of warfarin are also influenced by environmental factors such as diet, drug interactions, critical illness, etc. (4). Daily fluctuations in vitamin K-dependent factor VII levels, which were assumed to lead to the difference in stability of warfarin and acenocoumarol treatment, have been shown to occur with both drugs (10).

Unlike in our country, Bosnia and Herzegovina, where both drugs are available and prescribed, only one VKA is commonly available in most regions (11). Warfarin is the drug of choice in the United States, Scandinavia, and the UK, and is predominantly used in Italy. Acenocoumarol is commonly used in Spain, the Netherlands, and Poland. Phenprocoumon is primarily used in Germany, and fluindione in France (12). This may be the reason why data from post-marketing studies comparing the stability of warfarin and acenocoumarol treatments are still lacking.

Therefore, this study aimed to investigate which of the two VKAs, warfarin or acenocoumarol, leads to more stable anticoagulation control in patients with mechanical heart valves and atrial fibrillation.

Material and Methods

Study Design and Patients

This was a prospective, one-year clinical cohort study. Patient recruitment and data collection were performed at the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina (FB&H). The enrolment period was from May 2014 to May 2015.

Surgical implantation of a mechanical heart valve in our community is performed at the Clinical Center of Sarajevo University. Following implantation, an internist or cardiologist from the same department prescribes the initial lifelong anticoagulation therapy. After hospital discharge, the anticoagulation therapy of most of these patients is followed up and managed at the Institute under the care of transfusion specialists, and the remaining patients are followed up under the care of internists, cardiologists, or general practitioners at different healthcare institutions. Due to the lack of a centralized registry for these patients at the time of the study, this study included only patients who were followed up with anticoagulation therapy and managed at the Institute under the care of transfusiologists.

Patients were identified by accessing the electronic medical records of the Institute. The study inclusion criteria were age 15–80 years, a confirmed diagnosis of atrial fibrillation, at least eight months of warfarin/acenocoumarol treatment, regular monthly INR check-ups prior to study enrolment, no presence of acute thromboembolic event, and no planned surgery or diagnostic procedures requiring discontinuation of anticoagulation

treatment in the planned one-year study period. Eligible patients were then followed prospectively for one year with regular INR monitoring.

The minimum period of eight months of warfarin/acenocoumarol treatment was chosen to ensure that patients had completed the initial phase of dose titration and INR stabilization, which typically occurs within the first few months of therapy. This duration allows for a more reliable assessment of anticoagulation control and reduces the impact of early fluctuations that are common immediately after therapy initiation. Although there is no universally established minimum period defined in the literature, this approach is consistent with previous studies evaluating anticoagulation stability in patients with mechanical heart valves (13–15), where the inclusion of patients with at least several months of stable therapy is common practice.

Data Collection

Patient demographic and clinical data (sex, age, height, weight, body mass index (BMI), body surface area (BSA), medical and surgical history, list of concomitant drugs with the potential to affect INR values, and position of the mechanical heart valve) were collected from patients' electronic records and through medical interviews and were recorded in the case report form. Information on INR measurements (dates, INR values, drug doses, and dosing regimens) was collected from the patient's anticoagulant therapy card.

INR Measurement

Plasma was obtained from blood samples collected by venipuncture of the cubital vein into 1.8 ml test tubes containing 3.2% sodium citrate (Vacutainer, Becton Dickinson, United Kingdom). The blood samples were centrifuged (Laboratory centrifuge CENTRIC 322A, Slovenia) at room temperature at 3000 rpm for 15 minutes. Prothrombin time (PT) was measured using a hemostatic automated analyzer (ACL Elite Pro, Italy) with a commercial liquid calcium recombinant human tissue factor – thromboplastin reagent (RecombiPlasTin, ISI 1.03). The INR is calculated automatically according to the formula $INR=(PT\ ratio)^{ISI}$ (International Sensitivity Index) (16). Measurements and calculations were performed in the laboratory of the Department for Detection of Coagulation Disorders at the Blood Transfusion Institute of the FB&H. Based on the AHA/ACC and ESC/EACTS guidelines (1, 3), the target INR value (2.0–3.0/4.0) was determined for each patient depending on the mechanical heart valve position, prosthesis thrombogenicity, and risk factors.

Ethics Statement

The study protocol was approved by the Review Board of the University of Sarajevo Pharmaceutical Faculty (Approval No. 0101-1833/15). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all patients prior to their enrollment in the study.

Statistical Analyses

The data were analyzed descriptively. The number of INR measurements per patient per year, the number of INR measurements within the therapeutic range per patient, the time interval between successive INR measurements, and the INR values across 12 consecutive measurements were assessed for patients treated with warfarin and acenocoumarol. The stability of anticoagulation treatment was assessed using the TTR and the proportion of patients below predefined TTR thresholds (<60%, <65%, and <70%). The time in therapeutic range was calculated using Rosendaal's daily linear interpolation between consecutive INR measurements method over a predefined one-year observation period that assumes linear changes in INR between successive measurements to estimate the proportion of time spent within the target range (17). Continuous numerical variables were tested for the normality of their distribution. Normally distributed data are reported

as mean±standard deviation (SD) and not normally distributed data as median and interquartile range (IQR, Q25–Q75). Categorical variables are reported as numbers and percentages. Data analyses were performed using MS Excel.

Results

Of the 201 patients with mechanical heart valves identified in the community, 90 were excluded because their clinical data were not accessible, and 111 patients were identified by accessing the Institute's electronic medical records. Of these, 73 patients, mostly women, met the inclusion criteria, with 35 patients treated with warfarin and 38 with acenocoumarol. The remaining 38 patients were excluded due to the absence of a confirmed diagnosis of atrial fibrillation, duration of VKA treatment shorter than 8 months, or planned surgery or diagnostic procedures requiring discontinuation of anticoagulation treatment in the planned one-year study period (Figure 1).

The demographic and clinical characteristics and valve positions of patients in the warfarin and acenocoumarol groups are shown in Table 1.

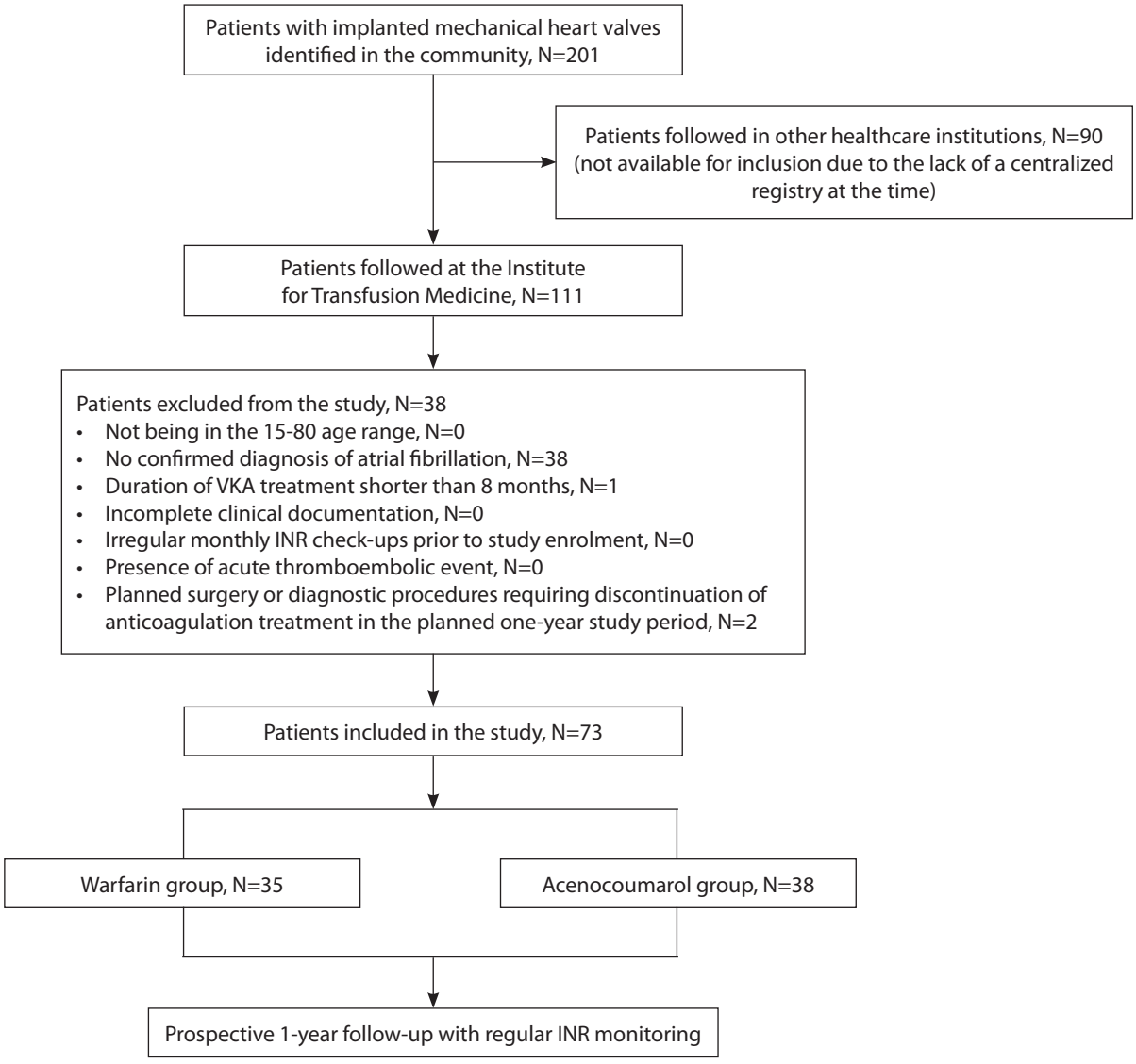

Figure 1. Flow diagram.

Table 1. Demographic and Clinical Characteristics of Patients in the Warfarin and Acenocoumarol Treatment Groups

Variable	Warfarin (N=35)	Acenocoumarol (N=38)
Sex (M/F)	12/23	15/23
Age (years)	63.71±9.60	58.71±11.97
BMI (kg/m^2)	26.89±3.61	26.07±3.53
BSA (m^2)	1.87±0.18	1.90±0.22
Mechanical valve position		
Aortic valve (N; %)	9 (25.7)	3 (7.9)
Mitral valve (N; %)	19 (54.3)	33 (86.8)
Both valves (N; %)	7 (20.0)	1 (2.6)
Unknown position (N; %)	-	1 (2.6)

M=Men; F=Women; BMI=Body mass index; BSA=Body surface area.

The patients in both groups were taking up to three concomitant drugs. The medications with the potential to increase INR values used in both treatment groups were amiodarone, digoxin (methyldigoxin), statins (simvastatin and atorvastatin), verapamil, allopurinol, propranolol, levothyroxine, acetylsalicylic acid, diclofenac, and vitamin E. The medications with the potential to decrease INR values used in both treatment groups were carbamazepine and spironolactone.

The mean number of INR measurements per patient per year was 11.05±1.87 in the warfarin group and 11.71±2.22 in the acenocoumarol group. The mean number of INR measurements within the therapeutic range per patient was 8.05±2.08 in the warfarin group and 7.21±2.17 in the acenocoumarol group. The mean time interval between successive INR measurements was 37.54±6.33 days in the warfarin group and 34.89±7.90 days in the acenocoumarol group.

All monthly median INR values across 12 consecutive measurements for warfarin (2.20–2.67) and acenocoumarol (2.14–2.68) were within the therapeutic range (Figure 2).

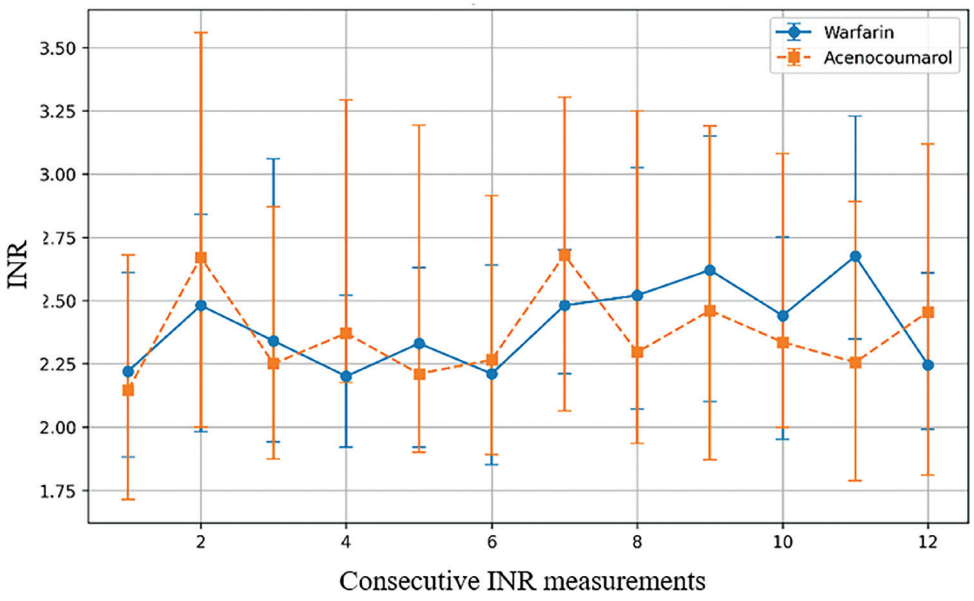

Figure 2. The monthly median with interquartile range (Q25–Q75) INR values for warfarin and acenocoumarol treatments across 12 consecutive measurements during a one-year observation period.

Table 2. Treatment Stability in the Warfarin and Acenocoumarol Treatment Groups

Variable	Warfarin (N=35)	Acenocoumarol (N=38)
TTR %, mean±SD	76.1±24.2	69.1±21.5
TTR <60	22.9	39.5
TTR <65	28.6	42.1
TTR <70	28.6	47.4

TTR=Time in therapeutic range; SD=Standard deviation.

The mean TTR was higher in patients treated with warfarin than in those treated with acenocoumarol, with better-quality anticoagulation being consistently more frequent in the warfarin group across all predefined TTR thresholds (Table 2).

Discussion

Our crude and descriptive results in patients with mechanical heart valves and atrial fibrillation, similar in sex, age, BMI, BSA, the number of used concomitant drugs known to interact with vitamin K antagonists, the number of INR measurements per patient, the number of INR measurements within the therapeutic range per patient, the mean time interval between successive INR measurements, and the mean INR values across consecutive measurements, showed that compared to acenocoumarol, warfarin treatment might have been associated with more stable anticoagulation i.e. with a higher mean time in the therapeutic range and a smaller proportion of patients being below all predefined TTR thresholds (<60%, <65%, and <70%).

Considering that a TTR of ≥65% is commonly accepted as a marker of INR stability, warfarin therapy demonstrated greater anticoagulation stability compared with acenocoumarol, as reflected by higher mean and TTR values and a lower proportion of patients with suboptimal TTR levels. Nevertheless, the overall mean TTR in the acenocoumarol group also exceeded the 65% threshold, indicating that satisfactory anticoagulation control was achieved with both VKAs in this cohort. Similar findings have been reported in other studies (6, 18, 19). When comparing TTR values across studies, it is important to acknowledge that different methodological approaches were used. While some of the cited publications applied Rosendaal's linear interpolation method, most commonly recommended given that it directly incorporates time (17, 18), others assessed anticoagulation quality using alternative approaches, i.e. using the Last Check in File method based on the last INR measurement of each month (10), or using the percentage of INR values within the therapeutic range (proportion-in-range method) without applying linear interpolation (6, 19, 20).

The recent Italian nationwide PLECTRUM study compared the quality of warfarin and acenocoumarol treatments in 2111 patients with mechanical prosthetic heart valves, of whom 1716 (81.3%) were treated with warfarin and 395 (18.7%) with acenocoumarol. Consistent with our results, the results of this study also showed better anticoagulation quality, i.e., longer mean TTR in patients treated with warfarin compared to those treated with acenocoumarol (61.6±19.4% vs. 56.1±19.2%) (18). This suggests that our observations align with findings reported in larger populations. The PLECTRUM study also showed a lower TTR on acenocoumarol in all subgroups of patients analyzed according to sex, hypertension, diabetes, age, valve site, atrial fibrillation, and INR range.

Although studies comparing the stability of warfarin and acenocoumarol treatment in patients with mechanical heart valves are lacking, similar studies investigating the stability of these drugs in patients with non-valvular atrial fibrillation or other indications have also suggested the advantage of warfarin over acenocoumarol (6, 19). To this end, an Italian retrospective case-control study documented both the percentage of INR values within the therapeutic range (72% vs. 67%, P<0.001) and the percentage of patients with ≥75% of measurements of INR in the therapeutic range (50.7% vs. 34.5%, P<0.05), which were significantly higher in patients treated with warfarin than in those treated with acenocoumarol (6). In addition, Olivia et al. showed that INR values were more frequently in the therapeutic range in patients treated with warfarin than with acenocoumarol (65.5% vs. 63.4%) (19). These findings are consistent with our

results in patients with mechanical heart valves and atrial fibrillation, as we also observed higher TTR values and a lower proportion of patients below the predefined TTR thresholds in the warfarin group than in the acenocoumarol group.

Samsa et al. (21) showed that, compared to primary health care, the therapeutic value of INR is more often achieved in specialized institutions (55–60% vs. 34–47%). Despite the satisfactory overall median TTR in our study, a considerable proportion of patients with mechanical heart valves and atrial fibrillation, particularly in the acenocoumarol group, remained below the 65% threshold, indicating that consistently stable INR control can still be challenging, even in specialized care settings. As mentioned above, patients with stable INR values should be monitored every four to eight or even twelve weeks (4, 5).

The mean time interval between the two successive INR measurements in our study was approximately 5 weeks, 37.54 days in the warfarin group and 34.89 days in the acenocoumarol group. In the study by Kulo et al. (20), the time between the two measurements in patients with non-valvular atrial fibrillation recruited from the same institution was 27.17 days. In contrast to our study, some studies did not confirm the advantage of warfarin (10, 20, 22). Barcellona et al. showed that warfarin did not appear to be better than acenocoumarol in terms of PTs within the therapeutic range per patient (10). Moreover, Kulo et al. showed better stability of acenocoumarol compared to warfarin treatment in a one-year observational clinical study in patients with non-valvular atrial fibrillation (37.6% vs. 35.7%) (20). In the same study, the proportion of INR values in the therapeutic range was higher in patients treated with acenocoumarol than in those treated with warfarin (53.62% vs. 51.77%).

The clinical relevance of our results is that they can help clinicians determine which of the two available VKAs may be more suitable for patients with mechanical heart valves and atrial fibrillation. Greater stability of anticoagulation predicts better safety, improved quality of life, as fewer INR controls are needed, and reduced healthcare costs.

Strengths and Limitations of the Study

Our study is the first to compare two VKAs, warfarin and acenocoumarol, in patients with mechanical heart valves to whom both treatments are equally accessible and prescribed. As, according to established guidelines, VKA therapy remains the standard and only anticoagulant option for these patients, with treatment patterns based on INR-guided monitoring and dose adjustments remaining the same over the past decade, our study population and findings may be of clinical relevance. However, this study has several limitations. First, a small sample size resulting from the lack of a centralized registry of patients with mechanical heart valves in our community; therefore, patients whose anticoagulation treatment was followed in other healthcare institutions were not available for inclusion, which may limit the generalizability of our findings. Second, as no standardized predefined criteria/clinical scoring system/laboratory parameter is used to systematically guide the initial internists' or cardiologists' decisions on the assignment of a specific patient to warfarin or acenocoumarol, the treatment decision is made largely based on their preference/prescribing habits, comorbidities, concomitant drugs, availability of each drug through insurance reimbursement or market supply, and the patient's ability to access the drug. However, we did not collect information on those factors that might have predicted assignment to one VKA over the other or the stability of anticoagulation control. As these factors could theoretically function as confounders, we missed the opportunity to adjust the model for confounding, and residual confounding cannot be excluded. Therefore, based on crude and unadjusted analyses, the reported results are rather descriptive and hypothesis-generating than causal and may be partially or entirely explained by factors not accounted for in the analyses.

Conclusion

In this prospective, single-center, one-year clinical cohort study, based on crude and descriptive results, better anticoagulation stability, with a higher

mean time in the therapeutic range and a smaller proportion of patients below the predefined TTR thresholds, was suggested in warfarin- compared with acenocoumarol-treated patients with mechanical heart valves and atrial fibrillation. However, these unadjusted findings only represent a population description and should be interpreted cautiously. To confirm and expand our findings, additional larger prospective clinical studies are needed in patients with mechanical heart valves, with or without atrial fibrillation.

What Is Already Known on This Topic:

The prevention of thromboembolic events in patients with mechanical heart valves requires lifelong oral anticoagulants. Although new oral anticoagulants are available, vitamin K antagonists (VKAs) remain irreplaceable in these patients. Maintaining optimal anticoagulation with VKAs is difficult due to their narrow therapeutic index, i.e., the need to achieve therapeutic INR values while balancing thrombosis and bleeding. Although dose-dependent, their effectiveness also shows significant individual variation over time. Maintaining stable anticoagulation depends not only on numerous clinical factors, including age, body weight, diet, comedications, comorbidities, and patient compliance, but also on genetic variations. Unlike in Bosnia and Herzegovina, where both drugs are equally available and prescribed, only one of the VKAs is commonly available in most other regions. This may be the reason why data from post-marketing studies comparing the stability of warfarin and acenocoumarol treatments are still lacking.

What This Study Adds:

The descriptive findings of this study support the hypothesis that compared with acenocoumarol, warfarin may provide more stable anticoagulation control in patients with mechanical heart valves and atrial fibrillation.

Authors' Contributions: Conception and design: ŠHT and AKĆ; Acquisition, analysis and interpretation of data: ŠHT, AM and AKĆ; Drafting the article: ŠHT and AM. Revising it critically for important intellectual content: ŠHT and AKĆ. Approved final version of the manuscript: AKĆ.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Sociodemographic Characteristics of Patients with Schizophrenia: A Comparative Study with Healthy Controls

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Abstract

Objective. This study aimed to assess selected sociodemographic characteristics of patients with schizophrenia and compare them with those of a healthy control group, as well as within the group of patients with schizophrenia. **Patients and Methods.** A retrospective observational study was conducted involving 400 patients with schizophrenia and 200 healthy controls from the Herzegovina-Neretva Canton. The diagnosis of schizophrenia was made according to ICD-10 criteria, and sociodemographic data were obtained through structured interviews. **Results.** Individuals with schizophrenia are more likely to be older, less educated, unemployed, single, and smokers compared to healthy controls. Among patients with schizophrenia, analyses controlling for age showed that gender was significantly associated with both age of onset and duration of illness, with significant gender-by-age interactions. Marital status was significantly related to age at onset and demonstrated a significant interaction with age in relation to illness duration. Education level was associated with age at onset but not with illness duration. No significant differences in illness onset were found across employment groups. **Conclusion.** Sociodemographic characteristics are closely associated with key clinical features of schizophrenia, including age at onset and illness duration. These findings highlight the importance of considering gender, marital status, and educational background when interpreting illness trajectories. The results further underscore the need for early intervention strategies, psychoeducation, and integrated social and healthcare support aimed at improving functional outcomes and quality of life for individuals with schizophrenia and their caregivers.

Key Words: Schizophrenia ▪ Sociodemographic Factors ▪ Quality of Life ▪ Urban Health.

Introduction

Schizophrenia is a highly complex psychiatric disorder that profoundly affects not only individuals with the condition but also society as a whole (1). It is conceptualised as a multifaceted psychiatric syndrome of unclear aetiology, characterised by marked heterogeneity in clinical presentation, symptom profiles, and levels of functional impairment (2, 3). As a severe mental illness resulting from disrupted brain function, schizophrenia leads to impairments in essential mental processes and behaviours, with substantial consequences for social, occupational, and family functioning (1). Although schizophrenia affects approximately 0.3–0.7% of people worldwide, its long duration, early onset, high disability weight, and associated functional impairment and mortality contribute to a disproportionately large burden of disease measured by Disability-Adjusted Life Years (DALY) and Years Lived with Disability (YLD). In this context, schizophrenia has been identified by the World Health Organization as one of the top global causes of disability, and contributes on the order of >10 million DALYs annually, placing it among the leading causes of disability in global burden assessments (4). Against this global background, epidemiological indicators of schizophrenia show considerable variability across regions and studies, influenced by methodological and contextual factors. Reliable epidemiological data

on the characteristics of schizophrenia in Bosnia and Herzegovina are currently lacking. Existing studies report annual incidence rates ranging from 10 to 70 per 100,000 population (5), while a meta-analysis by McGrath et al. identified a median incidence of 15.2 per 100,000 population per year (6). The disorder most commonly manifests in late adolescence or early adulthood and is often preceded by a prodromal phase lasting months or years, marked by gradual declines in cognitive and social functioning (3). Beyond its epidemiological features, schizophrenia is associated with persistent functional impairments that frequently extend into periods of symptomatic remission. Individuals with schizophrenia often experience difficulties in maintaining social relationships, sustaining employment, and achieving independent living. Functional outcomes are closely linked to the severity of cognitive and negative symptoms present at illness onset (7, 8). In this context, sociodemographic characteristics represent important indicators of social determinants of health, as they reflect the broader social and environmental factors that shape disease course, access to resources, and long-term outcomes. Comparing these characteristics with those of a healthy control group enables the identification of disparities that may contribute to functional limitations, reduced quality of life, and adverse health outcomes in individuals with schizophrenia (8).

The reform of mental health services in Bosnia and Herzegovina has shifted the organisation from traditional institutional care toward a community-based model, in which mental health professionals and community mental health centres play a central role in the prevention, treatment, and promotion of mental health, including care for patients with schizophrenia and their caregivers (9). Bosnia and Herzegovina has established a legal framework for employing people with mental disabilities, based on disability employment practices and supported by entity laws and rehabilitation funds. However, implementation is often hindered despite these legal regulations. Employment includes both institutional models and innovative non-institutional solutions developed with user associations (10).

Given the limited regional data and the importance of sociodemographic factors for understanding functional outcomes**,** the present study aimed to investigate selected sociodemographic characteristics in patients with schizophrenia and compare them with those of the healthy general population**.** A secondary aim was to examine these sociodemographic characteristics among patients with schizophrenia in relation to age, age at disease onset, and illness duration.

Patients and Methods

Study Population

This retrospective, observational, hospital-based case–control study included a total of 600 participants from the Herzegovina-Neretva Canton, comprising 400 patients with schizophrenia and 200 healthy controls, from January 2015 to May 2025.

Patients with schizophrenia were treated as either outpatients or inpatients at the Psychiatric Clinic of the University Clinical Hospital (UCH) Mostar. Eligible patients were consecutively identified from clinical records, provided that all required data were available. The diagnosis of schizophrenia was established according to ICD-10 criteria and confirmed using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (11). Only patients with a primary diagnosis of schizophrenia and without additional psychiatric comorbidities were included in the study.

The control group consisted of 200 healthy participants randomly selected from an existing hospital research archive. Controls were relatives or visitors of patients hospitalized for various psychiatric conditions, not limited to schizophrenia. All control participants were physically and mentally healthy, had no documented psychiatric or somatic illness for at least one month prior to inclusion, and were screened using the Mini-International Neuropsychiatric Interview (M.I.N.I.). No matching procedures were applied between patients and controls.

Methods

Sociodemographic data, including age, gender, education level, employment status, marital status, and place of residence, were collected from all participants using a structured questionnaire. For patients with schizophrenia, additional clinical variables, including age at disease onset and duration of illness, were recorded. Age at onset was defined as the age at first appearance of symptoms, while duration of illness was defined as the interval between symptom onset and the date of assessment. Although all assessments and questionnaires were administered at the time of hospital contact, the data were retrospectively extracted and analysed for the purposes of this study.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Clinical Hospital (UHC) Mostar (No: 204/25).

Statistical Analysis

Univariate and multivariate outliers for the dependent variables were examined, resulting in the exclusion of four multivariate and three univariate cases for age at illness onset. Normality was assessed using the Shapiro–Wilk test. Continuous variables were analyzed with t-tests or ANCOVA, and categorical variables with Chi-square or Fisher's exact tests. Means and standard deviations are reported for continuous variables, frequencies and percentages for categorical variables. Significant interactions between covariates and factors were probed using the Johnson–Neyman technique for two-level factors, and simple slope analyses with pairwise comparisons for factors with more than two categories. Statistical significance was set at $P<0.05$. Analyses were conducted in SPSS 20.0 (IBM Corp., Armonk, NY, USA) and jamovi 2.6 (The jamovi project, 2025).

Results

The study included 400 patients with schizophrenia (60.5% male, 39.5% female) and 200 healthy controls (56.5% male, 43.5% female). The mean age of patients with schizophrenia was 50.5±13.1 years, while the mean age of controls was 44.2±15.1 years. Among patients with schizophrenia, most had completed high school 67%, followed by university 12%, elementary school 11.3%, and no elementary school 3.3%. In terms of employment, 8.8% of patients were employed, 49.8% unemployed, 40% retired, and 0.8% students. Regarding marital status, 18.3% were married, 67.3% unmarried, 8% divorced, and 6.5% widowed. Most patients lived in urban areas 57.5%, and 69% were smokers. Patients with schizophrenia were older than those in the control group and exhibited statistically significant differences in education level, employment status, marital status, and smoking habits. No significant differences were observed in terms of place of residence or gender distribution. Regarding education level, the patient group included more individuals with no formal education or only elementary-level education, and fewer with a university degree, compared to the control group. Most patients were unemployed or retired, and the majority were single, divorced, or widowed. Patients were also more frequently smokers than controls (Table 1).

At the group level for participants with schizophrenia, mean age at illness onset was 27 years, while the mean for duration of illness was 21.1 years. The relationship between gender and age at illness onset varied as a function of participants' chronological age (significant gender × age interaction, $P=0.003$; Table 2).

Simple slopes analysis showed that among younger participants, men had an earlier illness onset than women, whereas among older participants, the pattern tended to reverse, with women showing a somewhat earlier onset than men. Overall, gender differences in age at onset diminished with increasing age.

Table 1. Comparison of Sociodemographic Characteristics between Patients with Schizophrenia and Healthy Controls

Characteristics	Group				Test	P
	Schizophrenia		Control			
Age	50.5±13.1		44.2±15.1		t=4.974*	<0.001
Gender N (%)						
Male	242	60.5	113	56.5	χ^2=0.883†	0.197
Female	158	39.5	87	43.5		
Education level N (%)						
No elementary school	13	3.3	1	0.5	χ^2=41.302‡	<0.001
Elementary school	45	11.3	13	6.5		
High school	268	67	129	64.5		
University	48	12	57	28.5		
Unknown education level	26	6.5	0	0		
Employment N (%)						
Employed	35	8.8	151	75.5	χ^2=126.664‡	<0.001
Unemployed	199	49.8	19	9.5		
Student	3	0.8	6	3.0		
Retired	160	40	24	12.0		
Unknown working status	3	0.8	0	0		
Marital status N (%)						
Married	73	18.3	124	62	χ^2=115.970‡	<0.001
Unmarried	269	67.3	63	31.5		
Divorced	32	8.0	6	3		
Widow/er	26	6.5	7	3.5		
Residence N (%)						
Urban area	230	57.5	132	66.0	χ^2=7.006‡	0.07
Countryside	162	40.5	68	34.0		
Unknown living area	8	2.0	0	0		
Smoking status N (%)						
Smoker	276	69	101	50.5	χ^2=36.907‡	<0.001
Nonsmoker	106	26.5	99	49.5		
Unknown smoking habits	18	4.5	0	0		

*Student t-test; †Fisher exact test; ‡Chi-square test.

Similarly, the association between age and duration of illness varied by gender (significant gender × age interaction, P<0.001). Simple slopes analyses indicated that among younger participants, women had a longer duration of illness than men, while among older participants, a longer illness duration tended to be observed in men.

Age at illness onset differed by marital status (significant main effect of marital status, P=0.026), with unmarried participants showing an earlier onset compared to married individuals. No other marital status group differences were observed (Table 3).

Although initial analyses suggested differences in illness duration across marital status groups, these differences were no longer significant after controlling for age. However, a modest age × marital status interaction was observed (P<0.045), indicating some variability in the age–duration relationship across marital status categories. Simple

Table 2. Differences among Patients with Schizophrenia, Controlling for Age

Variables	Variance	df	F	P	η^2
Age of onset	Age (covariate)	1	7.4	0.007	0.025
	Gender	1	12.566	0.000	0.042
	Gender×Age	1	8.829	0.003	0.030
	Error	286	-	-	-
Duration of illness	Age (covariate)	1	171.96	0.000	0.375
	Gender	1	22.192	0.000	0.072
	Gender×Age	1	31.344	0.000	0.099
	Error	290	-	-	-
Age of onset	Age (covariate)	1	0.100	0.752	0.000
	Marital status	3	3.140	0.026	0.032
	Marital status×Age	3	2.447	0.064	0.025
	Error	282	-	-	-
Duration of illness	Age (covariate)	1	40.209	0.000	0.125
	Marital status	3	2.413	0.067	0.025
	Marital status×Age	3	2.725	0.045	0.028
	Error	282	-	-	-
Age of onset	Age (covariate)	1	0.018	0.892	0.000
	Education	4	2.556	0.039	0.038
	Education×Age	4	2.125	0.078	0.032
	Error	261	-	-	-
Duration of illness	Age (covariate)	1	26.013	0.000	0.091
	Education	4	0.982	0.418	0.015
	Education×Age	4	1.355	0.250	0.020
	Error	261	-	-	-
Age of onset	Age (covariate)	1	14.209	0.000	0.048
	Work status	2	0.636	0.530	0.005
	Work status×Age	2	1.256	0.286	0.009
	Error	279	-	-	-
Duration of illness	Age (covariate)	1	88.019	0.000	0.240
	Work status	2	0.645	0.525	0.005
	Work status×Age	2	1.160	0.315	0.008
	Error	279	-	-	-

df =Degrees of freedom; F=F-statistic (ANOVA); P=Significance level; η^2 = Eta squared effect size.

slopes analyses did not reveal significant differences between individual groups.

Educational level was associated with age at illness onset (significant main effect of education, P=0.039), with participants without completed schooling exhibiting the highest age at onset (Table 3).

This effect was not moderated by age (non-significant education × age interaction).

In contrast, duration of illness did not differ across educational levels after controlling for age. Age remained a significant predictor of illness duration, with older participants showing longer illness duration, while neither the main effect of education nor the education × age interaction reached statistical significance (Table 2). Age at illness onset did not differ across work status groups after adjusting for age, as neither the main effect of

Table 3. Age of Onset and Illness Duration by Gender and Socioeconomic Characteristics, Controlling for Age

Variables	Categories	Age of onset M (CI)	Duration of illness M (CI)
Gender	Male	26.2 (25.03 – 28.4)	21.6 (20.4 – 22.8)
	Female	29.4 (27.8 – 31.02)	19.4 (17.8 – 21.1)
Marital status	Married	30.7 (28.2 – 33.1)	19.4 (16.8 – 22.1)
	Unmarried	26.6 (25.5 – 27.8)	20.8 (19.5 – 22.0)
	Divorced	28.6 (25.1 – 32.1)	18.01 (14.2 – 21.8)
	Widow/er	27.5 (19.3 – 35.8)	24.7 (15.6 – 33.7)
Education level	No education	43.2 (34.2 – 52.3)	23.1 (13.0 – 33.2)
	Elementary	28.3 (25.1 – 31.4)	19.7 (16.2 – 23.1)
	High school	27.0 (25.9 – 28.1)	19.5 (18.3 – 20.8)
	University	27.3 (23.8 – 30.8)	20.03 (16.2 – 23.9)
	PhD	22.1 (16.5 – 27.7)	25.1 (18.8 – 31.3)
Work status	Employed	28.1 (24.9 – 31.3)	19.7 (16.3 – 23.1)
	Unemployed	28.1 (26.7 – 29.5)	18.6 (17.1 – 20.1)
	Retired	26.6 (24.3 – 28.9)	21.9 (19.4 – 24.3)

M=Mean; CI=Confidence interval.

work status nor the work status × age interaction was significant.

Although initial analyses indicated differences in illness duration by work status, these differences were no longer evident when age was included as a covariate. Age remained the primary factor associated with illness duration, and no significant work status × age interaction was observed (Table 2).

Discussion

The sociodemographic factors investigated in this study provided us with a valuable framework for understanding the broader psychosocial challenges experienced by individuals with schizophrenia (12). In the group of patients with schizophrenia, there were more men than women, which is consistent with previous findings suggesting that men have a slightly higher incidence of schizophrenia than women, although some studies report that the risk of developing schizophrenia is similar between genders (12, 13). Although men and women have similar lifetime prevalence rates, men usually develop the illness 3 to 5 years earlier than women and tend to exhibit more pronounced negative symptoms, poorer social functioning, and a greater likelihood of co-occurring substance use disorders (14). As reported by Abel et al., the modal age of onset for schizophrenia is 22 years for both men and women; however, the overall distribution of age at onset varies between the sexes (15). Gender differences in the incidence and prevalence of schizophrenia largely depend on the strictness of the diagnostic criteria used. Specifically, when more flexible criteria are applied, these gender differences tend to be less pronounced. In our study, age of onset was significantly higher in women than in men of younger age. The difference in age of onset is consistent with prior reports (14, 15). Compared to males, females with schizophrenia typically have a later age of onset, better premorbid functioning, and a milder course of illness. They also tend to exhibit more affective and atypical clinical features, show fewer structural brain changes, and respond more favourably to social and occupational interventions. In addition to genetic predispositions for the development of schizophrenia, women appear to be more susceptible to environmental factors, such as *in utero* exposure to the influenza virus. Influenza epidemics and pandemics have been associated with a higher incidence of schizophrenia and affective disorders

among individuals exposed during the fetal period, particularly females. The differing disease manifestation in comparison to men has also been attributed to the influence of estrogen (16, 17). In patients with schizophrenia, the level of education has been used both as a measure of premorbid functioning and as a predictor of disease onset. Studies have shown that patients with higher levels of education tend to experience a later onset of illness, exhibit less pronounced psychotic symptomatology, and demonstrate generally better cognitive functioning (12, 18). Paradoxically, in our study, patients with lower levels of education had a statistically significantly higher age of disease onset; we suppose this may be due to a prolonged period of poor premorbid functioning or unrecognized early symptoms of the disease. Patients with schizophrenia were significantly more frequently unemployed compared to healthy controls. In Bosnia and Herzegovina, lower employment rates among patients with schizophrenia are partly influenced by social and financial support, including disability pensions and assistance for individuals with mental disorders. These local factors should be considered when comparing results with studies from other countries; however, our finding is consistent with previous studies demonstrating a notably lower employment rate among patients with schizophrenia compared to the general population (10, 19, 20). It is well established that the employment rate among patients with schizophrenia decreases over the course of the illness, whereas in the healthy population, this rate remains relatively stable over time. However, patients with schizophrenia did not vary in age of illness onset or illness duration regardless of their (un)employment status in our study. According to various studies, the employment rate in patients with schizophrenia varies widely, as different methodologies are used to define and assess employment. Some studies from Europe report employment rates ranging from 10% to 20% among patients with schizophrenia, which is similar to the findings of this study. Factors that negatively influence the employment rate among patients with schizophrenia include stigmatisation, discrimination, fear, and a lack of adequate professional support. Conversely, employment is associated with positive outcomes in social functioning, symptom severity, quality of life, and self-esteem (21). Patients with schizophrenia commonly exhibit impairments in multiple areas of daily functioning, which often persist even after remission is achieved. These difficulties affect their ability to maintain employment, live independently, and sustain social relationships. Even in symptomatic remission, individuals with schizophrenia may experience difficulties in everyday life (7, 22). Due to impairments in daily functioning, a large proportion of patients with schizophrenia belong to the lower socio-economic class. One possible explanation is that various aspects associated with this mental disorder limit opportunity for social achievement (23). As a result, unemployment and early retirement are highly prevalent among individuals with schizophrenia. It is well established that, compared to other mental illnesses, schizophrenia imposes the greatest burden in terms of social disability (24, 25). Schizophrenia is a disorder that, by definition, results in significant impairments in social and family functioning, which are factors that are crucial for initiating and maintaining marital relationships. In the present study, patients with schizophrenia were statistically significantly more likely to have never been married compared to healthy controls, which is consistent with previous studies reporting a lower prevalence of marriage among individuals with schizophrenia (21, 26). Our results additionally support this, while a significantly later illness onset is evident among married patients with schizophrenia than the unmarried group. This implies that the married patients might have had a milder illness course, which allowed for better social functioning. In the present study, no statistically significant differences were observed between patients with schizophrenia and healthy controls in terms of place of residence. However, a trend was noted, with 57.5% of patients living in urban areas compared to 66% of controls, which may suggest a minor local effect that did not reach significance. This finding suggests that, within our sample,

urban residence itself cannot be considered a distinguishing factor between patients and controls and should be interpreted with caution. Previous studies have indicated an association between living in urban areas and schizophrenia, although the nature of this relationship remains controversial. It is still unclear whether urban living increases the risk of developing schizophrenia or whether individuals with schizophrenia tend to migrate to urban areas. In the second half of the 20th century, this association was explained as a social drift of patients towards central city zones (27). Other studies have confirmed a link between being born and raised in urban areas and an increased risk of developing schizophrenia (28, 29). Previous research on this issue, despite employing varying methodologies for measuring urban exposure and using different definitions of schizophrenia, supports the conclusion that living in urban environments increases the risk of developing the disorder. According to a meta-analysis by Vassos et al., the risk of developing schizophrenia in the most urbanised areas is 2.37 times higher compared to the most rural areas (30). Similarly, Krabbendam and van Os reported that the risk of schizophrenia increases linearly with the degree of environmental urbanisation (31). Among the factors associated with urban living, several have been suggested as potential contributors to the increased risk of developing schizophrenia. These factors include the use of psychoactive substances such as cannabis, prenatal and perinatal health factors, poverty, levels of social stress, migration, environmental pollution, various infectious diseases, and vitamin D deficiency (32). Therefore, while existing literature strongly supports urbanicity as a population-level risk factor for schizophrenia, our findings do not allow for a direct confirmation of this association at the individual level. Differences in our study design, definitions of urban exposure, sample size, and local sociodemographic characteristics may partly explain this discrepancy. Frequent tobacco use is a well-documented and widely confirmed phenomenon among patients with psychosis, including those with schizophrenia. A 2019 study investigated the self-medication hypothesis and the role of smoking in alleviating distressing symptoms among individuals with psychosis. The results showed that 67% of patients with psychosis were smokers, compared to 25% of healthy controls (33). Wu et al. reported a notably high smoking prevalence (72%) among patients with schizophrenia experiencing acute and severe psychotic symptoms, which was higher than in individuals with other acute psychiatric conditions. In their study, smoking was associated with being male, younger age, lower educational attainment, shorter illness duration, comorbid substance use, and a shorter hospital stay. However, no significant association was found between smoking and illness severity, medication, psychiatric symptoms, or cognitive function (34). Patients with schizophrenia have a reduced life expectancy and an increased mortality rate, often accompanied by a higher prevalence of physical comorbidities, particularly cardiovascular diseases. Among the various contributing factors, smoking plays a significant role, negatively impacting physical health and increasing personal expenditures on tobacco products and medications (35). In this study, patients with schizophrenia were older than healthy controls, which may be a local phenomenon and could also reflect sample bias. Considering the age of disease onset, there were few younger participants below this threshold in the patient group compared to the healthy population, which could have influenced the result. That finding is not consistent with larger studies. Although they may be younger in chronological age, their biological age is higher than that of the general population. As a result, they experience more comorbidities and poorer health (36). In light of our findings, it is important to note that marital status, education, employment, and the observed associations with age should be interpreted cautiously, as they do not imply causal relationships.

It is also important to note that chronological age in the analyzed models may reflect cohort- or period-related effects rather than age-dependent biological mechanisms. Older patients in our sample likely belong to different diagnostic, treatment, and social cohorts, having been exposed

to distinct healthcare systems, societal attitudes toward mental illness, and availability of psychosocial support across different historical periods. Consequently, the observed associations involving age should be interpreted as reflecting generational or contextual influences rather than direct effects of biological ageing. This interpretation is consistent with the retrospective design of the study and with prior research emphasising the role of cohort and period effects in schizophrenia outcomes.

Patients with schizophrenia experience a poorer quality of life compared to the general healthy population. Reduced quality of life has been associated with unemployment, older age, engagement in occupations traditionally defined as female-dominated, financial difficulties, absence of marital partnership, and lower levels of education. Moreover, the quality of life of individuals who care for patients with schizophrenia is also significantly impaired, highlighting the need for various support programmes directed not only at the patients themselves but also at their caregivers (9, 10, 37). A key action for improving both the social status and quality of life of individuals with schizophrenia is education about mental illness, along with the destigmatisation of psychiatric disorders (38).

Limitations of the Study

Because of the retrospective design of the study, several potentially informative variables were not systematically recorded, including premorbid functioning, success in school, social and romantic relationship achievements, parental and caregivers' status, detailed socioeconomic circumstances, work-related accomplishments, and physical health. The inclusion of such data would have enabled a more nuanced and comprehensive appraisal of the quality of life in individuals living with schizophrenia. Also, long-term follow-up is recommended for such studies. The control group for this study was selected from visitors of patients hospitalized for various psychiatric conditions. Although this approach was intended to approximate characteristics of the general population and resulted in a heterogeneous control sample, it cannot be considered fully representative (complete mental and physical health is not characteristic of the general population). Potential selection bias related to shared urbanicity, environmental, or socioeconomic factors is therefore acknowledged. We suggest using a larger pool of participants from other hospital departments for studies that choose this type of control group.

Conclusion

This study highlights sociodemographic differences between individuals with schizophrenia and healthy controls. Patients with schizophrenia were generally older, less educated, more frequently unemployed, unmarried, and more likely smokers. After controlling for age, gender is significantly related to both age at onset and the duration of schizophrenia, highlighting the presence of gender-by-age interactions. Marital status was also associated with age at onset, with unmarried participants exhibiting earlier onset compared to married participants. Additionally, educational level was related to age at onset, as participants without completed schooling showed the highest age at illness onset compared to other education groups. It is important to note that these comparisons do not imply causal relationships. These findings underscore the importance of sociodemographic factors in understanding the clinical course of schizophrenia and emphasize the need for targeted psychosocial and educational interventions to improve outcomes and quality of life in this population.

What Is Already Known on This Topic:

Globally, schizophrenia is strongly associated with lower socioeconomic and sociodemographic status (SES), including reduced educational attainment, unemployment, and lower income. Evidence from large population-based studies indicates that both low parental and individual SES increase the risk of developing schizophrenia, while socioeconomic disadvantage among patients is linked to poorer cognitive, functional, and treatment outcomes. Furthermore, area-level SES interacts with individual disadvantage, with socially deprived individuals living in more affluent regions exhibiting particularly elevated risk. Overall, socioeconomic inequalities significantly influence both the onset and the course of schizophrenia worldwide (39-41).

What This Study Adds:

Although some research on mental health and schizophrenia has been conducted in Bosnia and Herzegovina (42, 43), there remains a notable lack of country-specific studies addressing the socioeconomic and sociodemographic profiles of individuals with schizophrenia, including aspects of risk, outcomes, and functioning. The present study contributes to filling this gap by providing a comprehensive analysis of the sociodemographic characteristics of patients with schizophrenia, based on a relatively large sample from this region. The most interesting finding in this study is the highest age of disease onset in the group of patients with the lowest education level.

Authors' Contributions: Conception and design: PR and MP; Acquisition, analysis and interpretation of data: PR, MP, JK and MPT; Drafting the article: JK and ADB; Revising it critically for important intellectual content: MPT and PR; Approved final version of the manuscript: PR and MP.

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Cervical Cytology and Age in HPV-Infected Women in North Macedonia: A Cross-Sectional Study

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Abstract

Objective. HPV infection is a key etiological factor in cervical epithelial alterations and neoplasia. Its prevalence and cytological impact vary with age, co-infections, and screening practices. This study investigated the association between HPV infection, age, and cervical cytological findings in women from North Macedonia. **Materials and Methods.** This cross-sectional study included 300 women aged 26–66 years, who were screened over a 13-month period (June 2023–July 2024). The participants were divided into two age groups (26–36 and 37–66 years). All participants underwent Pap testing, HPV screening, and microbiological evaluation. Ordinal regression analysis was used to examine the associations between age, microbial factors, and HPV positivity. **Results.** HPV prevalence was higher in the 37–66 group (12.33%) than in the 26–36 group (6.0%). However, younger age showed a stronger statistical association with HPV positivity (OR=2.10; P<0.1). Cytological abnormalities, particularly LSIL/CIN I, were more prevalent in HPV-positive participants. The use of conventional Pap smears was associated with lower HPV detection (OR=0.16; P<0.05). Co-infection with *Candida spp*. and atrophic inflammation were inversely associated with HPV positivity. **Conclusion.** This study confirmed the association between HPV infection and cytological changes, particularly in younger age groups. These results highlight the importance of age-tailored screening approaches and support the continued use of conventional Pap smears as cost-effective tools. Integrating virological and microbiological assessments may further refine cervical cancer prevention strategies, particularly in transitional healthcare systems across the Western Balkans.

Key Words: HPV ▪ Cervical Cytology ▪ Age ▪ CIN ▪ North Macedonia.

Introduction

Cervical cancer is a malignant tumor that develops in the transformation zone of the squamous epithelium of the cervix. It is the third leading cause of cancer-related deaths among women worldwide (1). The leading cause of cervical cancer is persistent infection with human papillomavirus (HPV), a sexually transmitted virus with double-stranded DNA (2). Of the more than 200 known HPV genotypes, 13 to 15 are classified as high-risk. HPV-16 and HPV-18 account for approximately 70% of cervical cancer cases (3, 4). Recent data from North Macedonia confirmed the prevalence of high-risk genotypes, including HPV-16, HPV-31, and HPV-51, which aligns with global trends (5). More recent international evidence has further strengthened the understanding that high-risk genotypes, such as 16, 18, 31, 33, and 52, remain the primary drivers of cervical carcinogenesis, with persistent infections posing the greatest oncogenic risk (6, 7).

Early diagnosis and regular monitoring are key to preventing and managing precancerous lesions and invasive cancers. The combination of HPV testing and cytological screening using the Papanicolaou test (Pap test) remains the standard for early detection (1, 8). Cytological evaluation helps identify morphological abnormalities

and provides insights into the pathophysiology of cervical dysplasia. Recent developments in digital pathology have further improved diagnostic accuracy and supported personalized clinical management (8). In addition, contemporary screening guidelines (WHO, ASCCP, ESGO) emphasize the biological significance of age, noting that HPV infection peaks in women aged 20–30 years, while after 35–36 years, positive HPV tests more frequently reflect viral persistence or latent reactivation rather than new infection, thereby carrying a different level of clinical risk (9).

Recent epidemiological data from the Institute of Public Health of North Macedonia (IPH) for the period January 1, 2023, to August 31, 2024, show a clear age-related pattern, with the highest incidence of high-risk genotypes—particularly HPV-16 (N=476), HPV-31 (N=242), HPV-53 (N=165), and HPV-18 (N=151)—identified in women aged 20–29 years (N=955) and 30–39 years (N=784), with a marked decline after the age of 40. These findings support the relevance of age-specific screening approaches and highlight the predominance of high-risk genotypes in younger populations (10).

This study aims to assess the prevalence of HPV infection in two age groups: 26–36 and 37–66 years. It will also examine the association with cytological findings and evaluate the risk of cervical intraepithelial neoplasia (CIN) and malignant transformation. Ordinal regression modeling will be used to identify the clinical and morphological factors that influence HPV positivity. By integrating updated epidemiological insights with local data, this study provides additional context for understanding age-specific HPV patterns in North Macedonia and contributes to the limited but expanding body of regional HPV research.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted between June 1, 2023, and July 31, 2024, at the "Indus Medika" Histopathology Laboratory in Skopje, North Macedonia, which is accredited by the Ministry of Health. A total of 300 women aged 26–66 years participated in the study. The participants were divided into two age groups: 26–36 and 37–66 years. All women provided written informed consent for participation before sampling. The age cut-off of 36 years was selected based on contemporary epidemiological evidence showing that HPV infection rates peak in early adulthood, while after 35–36 years, viral detection increasingly reflects persistent or latent infection, which is clinically associated with a higher likelihood of progression to CIN and other cervical abnormalities (11).

Sampling

Cervical epithelial samples were collected during routine gynecological check-ups, following standard sterile procedures. For molecular analysis (HPV-PCR), the sample was collected using a sterile cytobrush and stored in physiological saline (NaCl 0.9%) to preserve DNA integrity. For cytological examination (PAP test), the sample was collected using a plastic or wooden spatula and immediately spread on a glass slide for fixation and microscopic analysis.

All HPV samples were transported under controlled temperature conditions to ensure nucleic acid stability, following established molecular diagnostic guidelines.

Cytological Examination

The Papanicolaou test was used to detect precancerous and cancerous lesions of the cervix. The slides were fixed with cytological spray or 95% ethanol and stained according to the standard PAP test protocol (with hematoxylin, Orange G6, and Eosin-Azurin). The results were interpreted according to the Bethesda System, categorizing the findings into normal, low-grade intraepithelial lesion (LSIL), high-grade lesion (HSIL), and carcinoma. Cytological evaluation additionally included the documentation of koilocytosis, atrophy-associated inflammation, and microbial findings, such as *Candida* spp. and *Gardnerella vaginalis*, which may influence cervical epithelial susceptibility (12).

Viral DNA Isolation and Molecular Analysis

Viral DNA was isolated from epithelial samples using AmpliSens DNA-sorb-AM kits, which include cell lysis, silicone-based purification, and DNA elution. Real-time PCR was performed using the Neoplex HPV 29 reagent, based on the melting curve method, which allows the identification of 29 HPV genotypes. DNA extraction was performed following the manufacturer's protocol, including guanidine-based lysis, silica-column purification, ethanol washing, and final elution in TE buffer. Internal controls (ICc), negative controls (C–), and nuclease-free water were included in every batch to ensure analytical validity. The Neoplex HPV 29 multiplex PCR detects key high-risk genotypes commonly found in the region, including HPV 16, 18, 31, 33, 52, 53, and 56, ensuring comprehensive genotyping coverage (13).

Ethical Approval

This study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Tetova (Ref. No.: 09-297/1; Date: 25.02.2024). All procedures complied with the 2013 revision of the Declaration of Helsinki. The study adhered to standardized biosafety procedures and ensured the confidentiality and anonymization of all participant data.

Statistical Analysis

Cytological and molecular data were analyzed together to increase diagnostic accuracy. Statistical analyses were performed using SPSS and STATA v.14. Descriptive and inferential methods, including the chi-square test and ordinal regression models, were applied to assess the association between HPV status, cytological diagnosis, and age group. Model diagnostics included assessment of –2 log likelihood, Pearson and deviance goodness-of-fit statistics, and pseudo R^2 indices (Cox & Snell, Nagelkerke, McFadden), which indicated a modest but statistically interpretable explanatory capacity. Significance was set at $P<0.05$, with $P<0.1$ considered borderline due to biological plausibility.

Results

Data collected from the 300 women included in the study, divided into two age groups (26–36 and 37–66 years), included cytological and molecular assessment for human papillomavirus (HPV) infection. Analyses were performed in an integrated manner, assessing the distribution of infection by age group and the relationship with cytological diagnoses and risk factors identified through statistical analyses.

The prevalence of HPV infection was higher in the older group (37–66 years; 12.33%) than in the younger group (26–36 years; 6.00%). In addition, the majority of participants were HPV-negative, especially in the most advanced age group, where they constituted 61.33% of the total sample.

There is a clear disparity in the prevalence of HPV infection between the two age groups. Negative cases clearly predominate, especially in women over 36 years of age. The percentages presented in the graph help to visually interpret this distribution, reflecting the general trends of the first demographic analysis of the sample.

To ensure alignment with the data presented in Table 1, it is important to note that the frequency of cytological abnormalities follows a similar age distribution, with epithelial cell abnormalities and CIN more commonly observed in samples from the 37–66-year age group. This strengthens the observed association between HPV positivity and cytological changes.

HPV Status in Relation to Cytological Diagnosis and Age

To assess the relationship between HPV test results and cytological diagnosis in the study age groups, a comparative analysis was performed between HPV status (positive/negative) and PAP test findings. Table 1 presents the distribution of these data by age group and cytological category.

Table 1. Distribution of HPV Test Results in Relation to Cytological Diagnosis (Pap Test) and Age Group

Cytological diagnosis 26-36 Count		Age group (years)	Test			Total
		37-66	Negative	Positive		
		Count	Count	Count		
Epithelial cell abnormalities	1.0	8	41	41	8	49
Atypical squamous cells	1.0	3	20	19	4	23
Benign cells	1.0	0	29	26	3	29
Benign + atrophy	1.0	1	79	70	10	80
CIN (mild dysplasia)	1.0	6	15	13	8	21
Atrophy with inflammation	1.0	10	3	7	6	13
Post-colposcopy	1.0	2	5	3	4	7
Viral-associated changes	1.0	10	1	8	3	11
Gardnerella with colpitis	1.0	1	8	7	2	9
Candida + cocci	1.0	2	13	10	5	15
Normal smear	1.0	36	7	41	2	43

As shown in Table 1, cases with squamous epithelial abnormalities and mild dysplasia (CIN) are more common in the 37–66-year age group and show higher rates of HPV positivity. Specifically, 38.1% (8 of 21) of the samples diagnosed with CIN tested positive for HPV, suggesting a strong association between HPV infection and paraneoplastic changes in cervical cells.

The presence of atypical squamous cells (ASC) and cytological changes suggestive of viral infections (e.g., koilocytosis) were also more prominent in the older age group, reinforcing the potential role of persistent HPV infection in generating cellular atypia.

In contrast, benign smears, as well as those with associated atrophy and inflammation, were predominantly HPV-negative and most common in the 37–66-year-old age group, which corresponds to the perimenopausal and postmenopausal phases. However, to address the concerns of Reviewer 3, it should be emphasized that the distribution of microbial findings—such as *Candida* spp., *Gardnerella vaginalis*, and coccobacilli—was not uniform across the two age groups, and these patterns should be interpreted strictly within the context of Table 1. This clarification avoids overgeneralization regarding the association between microbial infections and HPV status.

Cytological findings in the 37–66 year age group were predominantly negative for intraepithelial lesions or any malignancy (NILM) and were often associated with atrophic changes and reactive cellular alterations caused by inflammation or fungal infections (e.g., *Candida spp*.). In contrast, the 26–36 year age group showed a higher frequency of epithelial abnormalities, including low-grade squamous intraepithelial lesions (LSIL) and cytopathic effects, suggesting a viral etiology (e.g., koilocytosis). These findings are consistent with the increased prevalence of HPV in this age group, supporting an association between younger age, HPV infection, and cytological atypia. Only HPV-positive cases are presented in Figure 1, divided by age group, reflecting the concentration of cytological diagnoses in this subpopulation.

The findings in Figure 1 indicate that HPV-positive individuals are more likely to present with epithelial abnormalities, particularly low-grade squamous intraepithelial lesions (LSIL), as well as atrophic changes associated with inflammation or cytopathic effects suggestive of the presence of the virus (e.g., koilocytosis). This observation is consistent with the age-specific distributions shown in Table 1, ensuring that the narrative corresponds directly with the quantitative data.

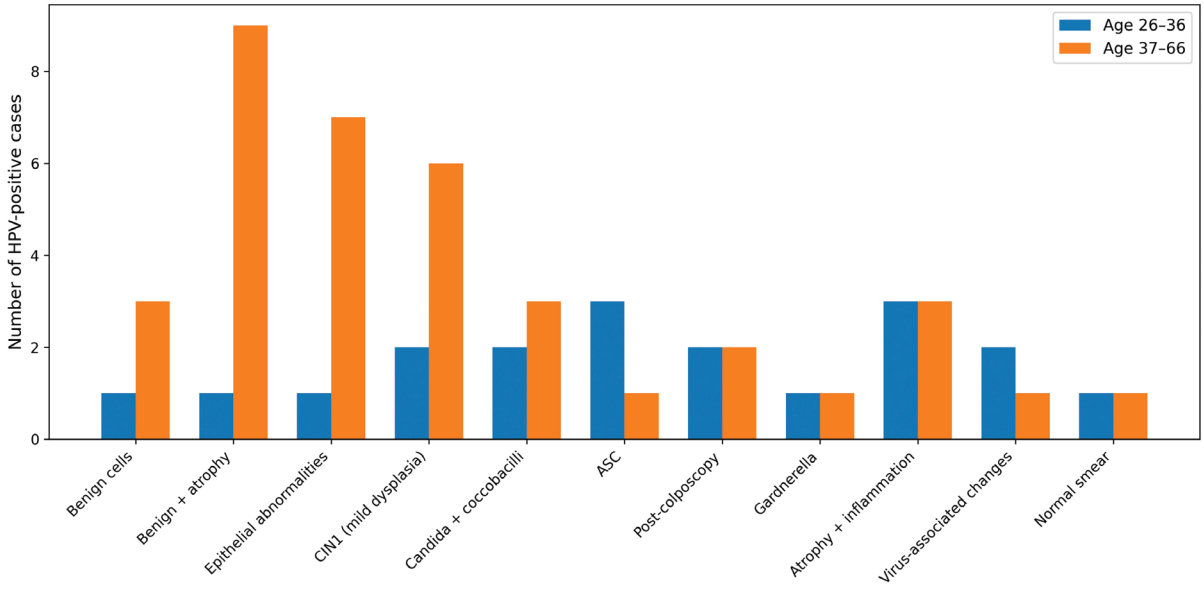

Figure 1. Cytological diagnoses among HPV-positive women by age group (N=55). Distribution of cytological findings in HPV-positive women, stratified into two age groups (26–36 years and 37–66 years).

Analysis of the Results of the Regression Model for HPV and Risk Factors

An ordinal logit regression model was applied to identify the independent factors associated with HPV positivity. The dependent variable was the HPV test result (positive or negative), and the independent variables included age group, presence or absence of epithelial dysplasia (CIN), presence of infections (e.g., candidiasis), colposcopy, presence of atrophy with inflammation, and performance of conventional smear tests.

The regression model used was as follows:

$P\ (\text{HPV positive}) = \beta_0 + \beta_1\ (\text{age } 26–36) + \beta_3\ (\text{CIN\_DISPLASIA} = 0) + \beta_4\ (\text{candidacy} = 0) + \beta_5\ (\text{colposcopy} = 0) + \beta_6\ (\text{conventional smear} = 0) + e_i$

The results of the regression analysis are summarized in Table 2.

Table 2. Coefficient Estimates, Statistical Significance Levels, and Odds Ratios for All Variables

Threshold	Parameter	Value	Standard error	Wald	df	Sig.	Odds
	[test=0.0]	-1.556	1.758	0.784	1	0.376	-
Location	[age=26-36]	0.743*	0.408	3.324	1	0.068	2.102
	[age=37-66]	0[a]	-	-	0	-	-
	[CIN 1 (Mild Dysplasia)=0.0]	-1.137†	0.501	5.163	1	0.023	0.321
	[CIN 1 (Mild Dysplasia)=1.0]	0[a]	-	-	0	-	-
	[Candida and Coccoid bacteria=0.0]	-1.045*	0.587	3.172	1	0.075	0.352
	[Candida and Coccoid bacteria=1.0]	0[a]	-	-	0	-	-
	[Check-up, colposcopy and HPV=0.0]	-1.932†	0.8	5.84	1	0.016	0.145
	[Check-up, colposcopy and HPV=1.0]	0[a]	-	-	0	.	
	[Conventional smear=0.0]	1.826†	0.81	5.082	1	0.024	6.209
	[Conventional smear=1.0]	0[a]	-	-	0	-	-
	[Atrophy with inflammation=0.0]	-1.113*	0.648	2.948	1	0.086	0.329
	[Atrophy with inflammation=1.0]	0[a]	-	-	0	-	-

a=Reference category (parameter set to zero); *P<0.001 statistically significant; †P<0.05 statistically significant.

As presented in Table 2, the regression models identified several factors that were statistically significantly associated with HPV positivity. The results showed that women in the 26–36 age group and those who did not undergo conventional Pap smear testing were significantly more likely to be HPV-positive. In contrast, the absence of CIN dysplasia, the absence of fungal infection, the absence of colposcopic control, and atrophy with inflammation were associated with a lower probability of HPV positivity. It is important to note that the explanatory power of the regression model is modest, as reflected by the pseudo R^2 values, indicating that additional clinical or biological factors not captured in the present dataset may contribute to HPV positivity. This clarification provides a more accurate interpretation of the model's performance without altering the statistical findings

Assessment of the Model's Goodness-of-Fit

To assess the explanatory power of the regression model, several statistical indicators were used, as presented in Tables 3–5.

Table 3. Model Fitting Information

Model	-2 log likelihood	Chi-square	df	Sig.
Intercept only	72.288	-	-	-
Final	43.351	28.937	6	0.000
Link function: Logit.				

Table 4. Goodness-of-Fit Assessment

Test	Chi-square	df	Sig.
Pearson χ^2	18.495	5	0.002
Deviance	18.333	5	0.003
Link function: Logit			

Table 5. Pseudo R-Square

Cox and Snell	0.092
Nagelkerke	0.150
McFadden	0.101
Link function: Logit	

The results in Table 3 show a significant improvement in the model with the inclusion of variables ($P<0.001$), suggesting a good statistical fit.

In Table 4, low P-values suggest an imperfect fit of the model, indicating that this model may not fully explain some of the real data. Despite the statistical significance of the model, as shown in Table 5, the low P-values suggest that the fit is not perfect and that the model explains a limited portion of the total variation (approximately 9–15%). Highlighting this explicitly ensures transparency and directly addresses the critique regarding low pseudo R^2 and borderline P-values.

Discussion

This study examined the association between HPV infection, cytological diagnoses, and age group in a selected population of women from various regions of North Macedonia. The results showed that while HPV prevalence was higher in the 37–66 age group, the younger group (26–36 years) had a stronger statistical association with HPV positivity in the regression analysis. This suggests that HPV infection may be more active in this younger group and is closely related to visible cytological changes (14, 15). Similar to the study by Shabani et al. (2025), who examined the distribution of HPV genotypes in women from North Macedonia (5), our study also confirms the prevalence of HPV in both reproductive and older age groups. While Shabani et al. reported that HPV-16 and HPV-31 were the most common genotypes (5), our findings show that these genotypes are linked to cytological changes, such as CIN and squamous epithelial abnormalities, especially among HPV-positive women (3, 16).

International studies support these results. A meta-analysis by de Sanjosé et al. (2010) found that HPV positivity is higher in younger women, whereas the rate of persistent lesions and invasive cancers increases with age (17). Similarly, Solomon et al. (2002) highlighted the importance of monitoring atypical cells, as they often indicate early-stage cervical HPV infection (18). Additionally, a review by Muñoz et al. (2003) confirmed that

regular cytological screening helps reduce HPV-related cervical lesions (8). In our statistical analysis, the factor "age 26 to 36 years" was positively associated with HPV positivity (OR=2.1; P<0.1), suggesting that this group is more biologically susceptible to infection. In contrast, having a normal conventional Pap smear was a significant protective factor, consistent with earlier evidence (8, 19).

Mild dysplasia (CIN I) was particularly associated with HPV-positive status, highlighting the oncogenic potential of some HPV genotypes in the absence of other microbial infections. Recent literature further reinforces that persistent high-risk HPV infection, especially with genotypes 16, 18, 31, 33, and 52, remains the strongest predictor of progression to CIN2+ and invasive cervical cancer (20, 21). Recent studies have also emphasized the role of the vaginal microbiome in modulating susceptibility to HPV persistence, particularly reductions in *Lactobacillus*-dominant flora and overgrowth of opportunistic species, which may influence epithelial vulnerability (22). These updated findings align with our observation that non-viral microbial changes were present but were not consistently associated with HPV positivity in our sample.

Interestingly, the presence of Candida spp. and atrophy with inflammation were associated with a lower chance of HPV positivity, which may suggest that the vaginal microenvironment plays a role in modulating viral infection (23, 24). However, contemporary evidence indicates that while fungal or dysbiotic changes may alter the inflammatory milieu, they should not be interpreted as protective factors without larger, controlled studies (22).

Limitations of the Study

One limitation of this study was the relatively small sample size and lack of HPV genotyping within this group, which makes a direct comparison with our previous work difficult. Additionally, we did not include other potentially influential factors in the analysis, such as immune status, sexual behavior, and hormonal contraceptive use, which could be significant confounders (25, 26). Future studies should aim to incorporate these variables to gain a clearer understanding of the many factors affecting HPV infection and cervical lesion development.

In addition, the cross-sectional nature of this study limits causal inference, as HPV persistence and lesion progression require longitudinal assessment. The single-center design restricts generalizability, as the sample collection was not representative of all regions of North Macedonia. Furthermore, although cytological and molecular analyses were integrated, the model's explanatory power remained modest, indicating that additional clinical, immunological, or behavioral factors—such as vaccination status or prior HPV exposure—may play a role but were not captured in the dataset. These limitations should be considered when interpreting the findings of this study.

Conclusion

This study confirms an association between HPV infection and cytological changes, especially in younger age groups. Normal smears and the absence of dysplasia were protective factors, whereas the presence of CIN and atrophy with inflammation were consistent with HPV positivity. Regular cytological screening and monitoring of risk groups remain essential for the early detection and management of HPV infection. These findings additionally underscore the relevance of integrating molecular HPV testing with cytological assessment, particularly in settings with limited resources, where combined approaches may enhance the early detection of cervical abnormalities. Furthermore, this study highlights the need for broader, multicenter research with larger sample sizes and longitudinal follow-up to better characterize HPV persistence, genotype-specific risk, and age-related patterns of cervical pathology (27).

What Is Already Known on This Topic:
HPV is the main etiological factor of cervical cancer. Prevalence and lesion severity vary by age.

What This Study Adds:
This study highlights the differences in HPV prevalence and cytological patterns between younger and older women in North Macedonia. It also identifies the protective effects of Candida-related inflammation and atrophy against HPV.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Criterion Validity of the Yale Physical Activity Survey (YPAS) in Croatian Older Adults

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Abstract

Objective. The Yale Physical Activity Survey (YPAS) is one of the most commonly used questionnaires to assess physical activity (PA) levels in older adults. Although previous studies have explored its validity properties against accelerometry, to date, no evidence has been provided in Croatian older adults. Therefore, the primary purpose of this study was to examine whether the YPAS is a valid tool for measuring PA levels. **Materials and methods.** A total of 46 older women (mean age 72.3±1.2 years) were recruited from three randomly selected public residential aged-care facilities. During the first stage, all participants wore a triaxial GENEActiv accelerometer on their non-dominant hand for 7 consecutive days. After the wearing period, the participants completed the YPAS questionnaire. The correlations between the YPAS and GENEActiv data were calculated using Spearman's order-rank coefficients. **Results.** The YPAS total PA was positively and moderately correlated with the number of steps, light and moderate PA, and moderate-to-vigorous PA (MVPA; ρ=0.48–0.64), yet a low positive correlation was found with vigorous PA (ρ=0.33). The YPAS total energy expenditure (EE) and the number of stairs performance showed similar correlation patterns with GENEActiv accelerometry data as the total PA (ρ=0.33–0.64). The summary index score exhibited moderate and positive correlations with the number of steps, light, moderate, and vigorous PA and MVPA (ρ=0.28–0.49). **Conclusion.** This study shows that the YPAS is a valid tool for assessing PA patterns in older Croatian adults.

Key Words: Aged ▪ Motor Activity ▪ Surveys and Questionnaires ▪ Energy Metabolism ▪ Croatia.

Introduction

In recent decades, population ageing has become a major global challenge, driven by increased life expectancy and improved living conditions (1, 2). As a result, maintaining health, functional capacity, and independence in older adults has become a key priority for healthcare systems (3). Despite increased longevity, older adults have a higher prevalence of non-communicable diseases and mental health risk factors compared to younger populations (4), underscoring the need for effective strategies to promote healthy ageing (5, 6).

Non-pharmacological interventions, particularly regular physical activity (PA), represent a cornerstone of disease prevention and health promotion in older adults (7-10). A substantial body of evidence demonstrates that regular PA positively affects physical health, cognitive function, functional capacity, and overall successful aging (11-13). Accordingly, the World Health Organization recommends that older adults engage in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity PA per week, along with muscle-strengthening activities on two or more days weekly (12). Despite these well-established benefits, the prevalence of physical inactivity continues to increase, especially among individuals aged 60 years and older (14). This trend toward sedentary behavior is associated with declines in muscle strength and functional performance, leading to an increased risk of adverse outcomes, such as falls, fractures, and hospitalizations (15).

Regular PA can be measured using objective measures, such as direct calorimetry, doubly labelled water, and motion sensors, including accelerometers, pedometers, and heart rate and oxygen consumption monitors (16). Although these approaches have gained popularity by providing reliable and valid PA data in various populations of older adults (16), they do not apply to population-based studies due to the disadvantages of high costs, time consumption, and limited availability of resources. In the absence of objective measures, subjective methods, such as questionnaires and activity diaries, are widely used to assess different types and intensities of PA (16). Their low cost, ease of administration, and shorter data collection time make them particularly suitable for large-scale studies and routine screening. However, subjective measures generally demonstrate lower validity compared to direct methods, a limitation that may be more pronounced in older adults due to age-related declines in health status, motivation, and PA patterns (15-17).

Commonly used PA questionnaires in older populations include the Physical Activity Scale for the Elderly (PASE), the Community Healthy Activities Model Program for Seniors (CHAMPS), and the International Physical Activity Questionnaire (IPAQ) (18-20). Nevertheless, these instruments have limited ability to capture household and light-intensity activities, which constitute a substantial proportion of daily PA in older adults (21). To address this limitation, Dipietro et al. developed the Yale Physical Activity Survey (YPAS), an interviewer-administered questionnaire designed specifically for older populations, enabling detailed assessment of PA type, intensity, and temporal patterns, including light-, moderate-, and vigorous-intensity activities (15, 22).

To date, the validity of the Yale Physical Activity Survey (YPAS) has been examined in several studies conducted in the United States, Africa, and higher-income European countries (15, 22-30). These studies generally reported low-to-moderate correlations between YPAS scores and accelerometer-derived measures of PA. Variability in validity estimates has been attributed to methodological differences in accelerometer placement and intensity cut-off values, particularly in relation to the assessment of light-intensity activities, which predominate in older populations (31, 32). Although the Croatian version of the YPAS has demonstrated satisfactory translation and reliability properties in older adults (32), its criterion validity has not yet been investigated.

Therefore, the primary aim of this study was to examine the criterion validity of the YPAS in a sample of Croatian older adults by comparison with accelerometer-based measures of PA. Based on previous findings (22-24), we hypothesized that YPAS outcomes would demonstrate low-to-moderate validity in relation to objective PA measures.

Materials and Methods

Study Participants

This observational, cross-sectional study enrolled 46 community-dwelling women from three randomly selected public residential aged-care facilities in the city of Zagreb, Croatia, from March 2024 to May 2024. The inclusion criteria were as follows: i) older adults aged ≥65 years, ii) free of locomotor and cognitive conditions, iii) free of recovering from acute illness, and iv) walking independently and without aid. The Montreal Cognitive Assessment (MoCA) scale was used to screen for initial thinking and resolving problems, and a score of 27 was used as a cut-off for individuals without cognitive problems (33). Given the observational and exploratory nature of this criterion validity study, a post hoc sensitivity power analysis was conducted using G*Power to determine the minimum detectable effect size based on the final sample size. Assuming a two-tailed correlation analysis, an alpha level of 0.05, and a statistical power of 0.80, a total sample size of 46 participants was sufficient to detect a moderate correlation coefficient (ρ=0.35). This effect size is consistent with previously reported validity coefficients in YPAS validation studies comparing questionnaire-based and accelerometer-derived physical activity measures (22-24). All analyses performed in this study were anonymous and followed the regulations of the Declaration of Helsinki (34).

The YPAS Questionnaire

The YPAS was designed to i) capture the time spent in various specific physical activities, grouped into five categories (housework, yardwork, caretaking, exercise, and recreation activities), and ii) assess the level of participation in different types of physical activities (22). The first part included a list of 27 activities, and each participant was required to indicate the time spent on each activity during the week, which was summed to provide the total PA time. To calculate the energy expenditure (EE), the time spent on each activity was multiplied by the corresponding intensity code and summed to obtain the overall EE. The second part included five PA dimensions related to the vigorous, walking, moving, standing, and sitting indexes. Each activity was multiplied by a specific weight factor from 1 (sitting) to 5 (vigorous) to calculate the individual indexes. The summary index was obtained by summing all the indices (22). The YPAS also provided data on the number of steps (10 stairs = 1 flight) taken daily, which was included in the validation model. The YPAS showed satisfactory test-retest reliability (α=0.70–0.92) and translational properties in a sample of Croatian older adults (35).

Validity

To assess the validity of the YPAS, we compared the results with those obtained using a GENEActiv accelerometer (Activinsights Ltd, Cambridge, UK) (36). The GENEActiv accelerometer was placed on the non-dominant arm for 7 consecutive days. Each participant was instructed to wear the device throughout the day (including while sleeping) and to keep daily logs to report the wearing and non-wearing times. It consists of three axes and has a seismic acceleration sensor that is small (36×30×12 mm), light (16 g), waterproof, and offers body temperature data to improve the confirmation of energy consumption and non-wear time. Research has shown a strong correlation between the GENEactiv monitor and indirect calorimetry (Pearson's r=0.79 to 0.98) (36). The GENEActiv was set to record at a rate of 80 Hz. To determine the number of steps and intensity of PA, the body posture and position of the arm on which the monitor was placed were assessed. If the heights recorded were greater than 15° below the horizontal, it meant that the wrist was raised, and if the arm position was less than 15° from the horizontal, it indicated a sitting or supine position. A degree of less than 15° below the horizontal represented the arm hanging more vertically and defined a standing position (37). The metabolic equivalent (MET) values were presented as weekly means and categorized as sedentary behavior (<1.5 METs), light (1.5–2.99 METs), moderate (3.0–5.99 METs), and vigorous (≥6 METs) PA levels (38). A cut-off of ≥3 METs indicated moderate-to-vigorous PA (MVPA). After 7 days, all participants returned the accelerometer and completed the YPAS.

Ethics Statement

Ethical approval was obtained from the Ethics Committee of the Faculty of Kinesiology at the University of Zagreb. This study did not receive any external funding.

Statistical Analyses

The Kolmogorov-Smirnov (K-S) test was used to examine the normality characteristics. Basic descriptive statistics of the study participants are presented as mean and SD or median and interquartile range (IQR) for normally and non-normally distributed variables. As the data did not follow a normal distribution, the correlation between the YPAS and actigraphy data was determined using Spearman's rank-order correlation (ρ). The size of a correlation coefficient was determined by the rule of thumb (39) as follows: i) negligible (0.0–0.3), ii) low (0.3–0.5), iii) moderate (0.5–0.7), iv) high (0.7–0.9), and v) very high (0.9–1.0). All procedures performed in this study were calculated using the Statistical Package for Social Sciences (SPSS, ver. 26, IBM Corporation, Chicago, IL).

Results

A total of 46 community-dwelling older women participated in this study. The general characteristics of the participants are presented in Table 1.

Table 2 presents the YPAS and GENEActiv accelerometry data on PA. According to the YPAS, women spent approximately 17.0 hours in total PA, and the total EE derived from different physical activities was approximately 76.0 kcal·min^{-1}. For the GENEActiv accelerometry data output, women spent 5.5 hours in light PA, 1.3 hours in moderate PA, 0.01 hours in vigorous PA, and 1.3 hours in MVPA.

The correlations between the YPAS and GENEActiv accelerometry data are presented in Table 3 and Figure 1. The YPAS total PA was positively and moderately correlated with the number of steps, light and moderate PA, and MVPA (ρ>0.45, P<0.001), but a low positive correlation was found with vigorous PA. The YPAS total EE and number of stair performances showed similar correlation patterns with the GENEActiv accelerometry data as the total PA. The summary index score exhibited moderate and positive correlations with the number of steps, light, moderate, and vigorous PA, and MVPA (0.25≥ρ≤0.5, P<0.05).

Table 1. Baseline Characteristics of Participants

Study variables*	Women (N=46)
Age (years)	72.3±1.2
Height (cm)	160.2±5.8
Weight (kg)	69.4±10.8
BMI (kg/m^2)	27.0±3.5
Education (years)	13.6±2.2
MoCA (scale)	27.2±0.9

*Values are presented as mean ± SD.

Table 2. Characteristics of PA Derived from the YPAS and GENEActiv Accelerometry Data (N=46)

Study variables	Mean (SD)	Median (IQR)	Min - max	Range
YPAS				
Total PA time (min·week^{-1})	17.1 (6.8)	15.0 (12.5– 20.8)	8.0–43.6	35.6
Total EE (kcal·min^{-1})	79.2 (36.2)	69.5 (56.2–93.8)	42.8–258.2	215.4
Summary index (score units)	35.3 (19.0)	29.0 (22.0–50.0)	13.0–114.0	101.0
Stair climbing (n)	44.4 (34.6)	30.0 (20.0–65.0)	10.0–140.0	130.0
GENEActiv accelerometry				
Number of steps (n/week)	8847.9 (4251.0)	8582.7 (6175.7–10,408.7)	1460.9–21027.1	15966.3
Light PA (min/week)	331.2 (94.5)	329.6 (289.1–400.2)	100.9– 529.0	428.1
Moderate PA (min/week)	75.7 (51.9)	61.6 (41.2–98.6)	5.9–221.4	215.5
Vigorous PA (min/week)	0.6 (1.5)	0.0 (0.0–0.4)	0.0–9.5	9.5
MVPA (min/week)	76.3 (52.8)	61.6 (41.2–98.8)	5.9–231.0	225.1

PA=Physical activity; YPAS=Yale Physical Activity Survey; EE=Energy expenditure; MVPA=Moderate-to-vigorous physical activity; SD=Standard deviation; IQR=Interquartile range; Min=Minimum; Max=Maximum; N=number.

Table 3. Criterion-Related Validity Between the YPAS and GENEActiv Accelerometry Data (N=46); The Data are Presented as Spearman's Correlation Coefficients (ρ)

Study variables	GENEActiv accelerometry				
	Number of steps (n/week)	Light PA (min/week)	Moderate PA (min/week)	Vigorous PA (min/week)	MVPA (min/week)
YPAS					
Total PA time (min·week^{-1})	0.64*	0.48*	0.58*	0.33‡	0.59*
Total EE (kcal·min^{-1})	0.64*	0.48*	0.59*	0.33†	0.60*
Summary index (score units)	0.49*	0.28‡	0.36†	0.29‡	0.37†
Stair climbing (n)	0.64*	0.34‡	0.60*	0.35†	0.60*

*P<0.001, †P<0.01; ‡P<0.05.

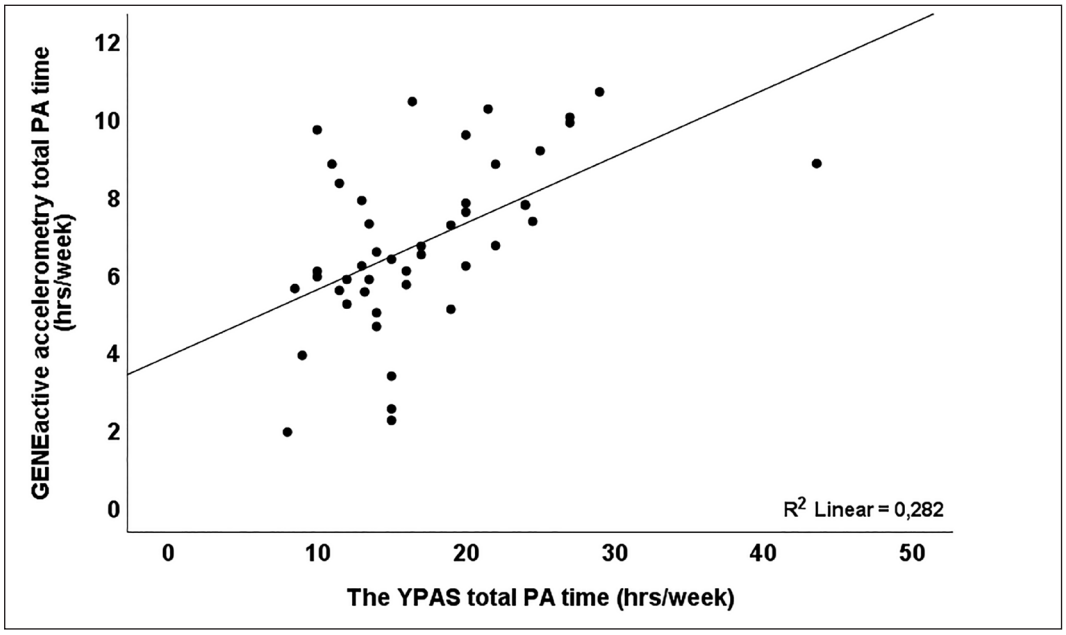

Figure 1. Correlation between the YPAS and GENEActiv accelerometry total PA time (hrs/week).

Discussion

The primary purpose of this study was to investigate the validity properties of the YPAS questionnaire in a sample of Croatian older adults. The findings indicate low-to-moderate positive correlations between the YPAS and accelerometer-based data. The largest correlations were observed between the YPAS outcome variables and the number of steps per week and MVPA.

Based on the study by Terwee et al. (40), the correlation of PA between subjective and objective methods should be above 0.5 to indicate acceptable validity properties. We found that total PA time and EE had moderate correlations with the number of steps, light and moderate PA, and MVPA, and a moderate (ρ=0.55) correlation between total PA time from the YPAS and GENEActive accelerometer, which is in line with previous studies (22-25). For example, a study by Dipietro et al. (22) showed a moderate correlation between the YPAS summary (*r*=0.58) and vigorous (*r*=0.60) index with maximal oxygen uptake. Similar findings have also shown that the summary index derived from the YPAS moderately correlated with MVPA (*r*=0.51) and accelerometer counts (*r*=0.45), while total time of PA correlated somewhat poorer with accelerometer-derived MVPA (*r*=0.41) (41). One study compared ankle- and waist-positioned accelerometer data with the YPAS and showed that total PA derived from both measures had moderate correlations, ranging from 0.36 to 0.59 (ankle) and 0.42 to 0.61 (waist) (42). However, the correlation coefficients obtained in this study were moderate (almost strong), which is inconsistent with other studies aiming to define the validity properties of the YPAS (25, 27). In a study by Young et al. (23), weekly EE and total PA time had lower correlations with daily EE from accelerometers (*r*=0.37). In addition, the total EE index (*r*=0.30), summary index (*r*=0.36), and total PA time (*r*=0.27) showed low-to-moderate correlations with total weekly EE (24). In Spanish older adults, the validity of total PA time (*r*=0.20), total EE (*r*=0.23), summary index (*r*=0.24), leisure walking index (*r*=0.26), and moving index (*r*=0.31) had low correlation properties against accelerometers (27). A recent study conducted among Polish older adults only reported a significant positive correlation between the YPAS- and accelerometer-derived total EE (*r*=0.23), while other components of the YPAS were not significantly correlated with the accelerometer data output (43). In older

adults from Portugal, a study by Domingos *et al.* (44) exhibited low-to-moderate correlations between the YPAS vigorous index (r=0.42) and total PA time (r=0.23) using the Xiaomi Mi Band 2® motion-tracking device, and low agreement between the two methods.

The discrepancies in the correlations across studies may be explained by several factors. Although we included studies that used the YPAS questionnaire, the actigraphy characteristics remained relatively heterogeneous. Despite the intention to measure the acceleration properties of an individual, some studies have used uniaxial (26, 44) or smartwatch monitor trackers (44) instead of triaxial accelerometers (29). Second, different cutoff values have been adopted to characterize the volume and intensity of PA. For example, a few studies have set accelerometer data based on Freedson's equation to measure activity counts, total activity, and total PA (41). However, it has been argued that such an approach may be too high for detecting low-intensity PA (41). Another study using the SenseWear® Pro2 Armband monitor defined any, light, or moderate PA to be set at ≥1.4, ≥2.5, and ≥3.6 MET (45), which is comparable to our study of any (≥1.5 MET), light (<3 MET), moderate (≥3 - <6 MET), and vigorous (≥6 MET) PA. For the YPAS, it is possible that participants overestimated the time spent in PA (particularly moderate and vigorous PA) based on their perceived exertion. We reported a moderate correlation between the total time of PA (r=0.60) from the YPAS and GENEActiv data. However, the mean total time of PA from the YPAS was 16.9 hours, compared to 6.7 hours from actigraphy, indicating a large overreporting of total PA (mean diff.=10.2 hours, 95% CI 8.5 - 11.9 hours, P<0.001). Third, previous studies have placed accelerometers on the hip (26, 43). Since accelerometers project PA counts from body movements, the hip region of the body may not be sensitive enough to capture lower-intensity PA (31). Older adults engage mainly in light PA (32), as confirmed in this study, where they spent approximately 5 hours in light-intensity PA, as opposed to moderate (1.25 hours) or vigorous (0.06 hours) PA. Thus, arm placement may be a better option for measuring light PA in older adults, as it provides better calibration and cross-validation properties than the hip (46). Finally, the higher correlation coefficients in this study may be attributable to the wearing time of the accelerometer. In contrast to other accelerometers, GENEActiv is a waterproof device that should not be removed during physical activities in water. This advantage was highlighted in a study by Król-Zielińska et al. (43), in which the majority of participants showed participation in water activities, which could have influenced the validity of PA derived from accelerometers.

Limitations of the Study

This study has several limitations. Due to its cross-sectional design, causal relationships between YPAS outcomes and GENEActiv accelerometer data cannot be established. However, standardized testing procedures consistent with previous validation studies were applied, with the YPAS questionnaire administered after a 7-day accelerometer assessment period, thereby minimizing potential measurement bias (43). A further limitation is the relatively small sample size (N=46), which restricts the generalizability of the findings to other older adult populations. In addition, the study included only female participants within a relatively narrow age range. This approach was adopted following statistical review recommendations, as the original sample included an insufficient number of male participants for reliable sex-based analyses. Consequently, the findings should be interpreted with caution and generalized primarily to community-dwelling older women with similar demographic and functional characteristics. Finally, the sample predominantly consisted of physically active older adults. Given that physically active individuals may be less prone to overreporting physical activity (46), caution is warranted when interpreting the results, particularly in relation to less active or sedentary older populations.

Conclusion

In summary, this study shows that the YPAS is a valid tool for assessing the total time of PA and EE during the week, summary index, and stair climbing related to accelerometer-derived PA. Most correlations yielded moderate power, indicating adequate validity properties. However, we recommend using the YPAS with caution, as it tends to overreport the total PA time in physically active older adults.

What Is Already Known on This Topic:

The Yale Physical Activity Survey (YPAS) is one of the most frequently used self-reported instruments for assessing physical activity patterns among older adults. Previous validation studies conducted in the United States and several high-income European countries have demonstrated low-to-moderate correlations between the YPAS scores and accelerometer-derived physical activity data. Although the questionnaire captures various types and intensities of activity, its accuracy may be influenced by the placement of accelerometers, activity cut-off points, and the tendency of older adults to overestimate their physical activity levels. Despite its translation and reliability testing in Croatia, the criterion validity of the YPAS has not yet been evaluated in older Croatian adults.

What This Study Adds:

This study provides the first evidence on the criterion validity of the Croatian version of the Yale Physical Activity Survey (YPAS) against triaxial accelerometry in older adults. The results demonstrate moderate positive correlations between YPAS-derived total physical activity, energy expenditure, and summary index with accelerometer-based activity measures. These findings indicate that the YPAS is a valid instrument for assessing physical activity patterns in older Croatian adults, although it may overestimate total activity time in physically active individuals.

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Workplace Violence Against Nurses in Croatia: A Cross-Sectional Study on Its Frequency, Impact, and Solutions

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Abstract

Objective. This study aimed to analyze the frequency of workplace violence against nurses in Croatia, its psychological consequences, and existing institutional measures to address this issue. **Materials and Methods.** A cross-sectional online survey was conducted among Croatian nurses in October and November 2023 using a convenience sample recruited via a social media platform. The questionnaire included 38 closed-ended questions covering socio-demographic data, experiences of physical, verbal, and sexual violence, and measures implemented to prevent or address workplace violence. **Results.** A total of 318 nurses participated in the study. Most participants (70%) reported experiencing some form of workplace violence in the past 12 months. Verbal violence was most frequent (66%), followed by physical (21%) and sexual violence (13%). Patients were the most common perpetrators of physical violence (84%), followed by relatives and healthcare staff. No statistically significant differences were found between the reporting of violent incidents and the level of nurses' education, nor between the intensity of psychological consequences and years of nurses' work experience. Nearly half of the participants (48%) stated that no formal measures existed in their workplace to prevent or respond to violence. **Conclusion.** Among nurses participating in this study, workplace violence was frequently reported, while work experience was not associated with psychological consequences. The findings indicate that workplace violence remains a relevant issue and may inform future efforts to improve preventive measures in healthcare settings.

Key Words: Nurses ▪ Violence ▪ Workplace ▪ Psychological Consequences ▪ Patients.

Introduction

The National Institute for Occupational Safety and Health (NIOSH), as part of the Centers for Disease Control and Prevention (CDC), defines workplace violence as violent acts (including physical assaults and threats of assaults) directed toward persons at work or on duty (1). Healthcare workers (HCWs) globally face a high risk of workplace violence compared to other professions and workplaces. According to the WHO, between 8% and 38% of HCWs suffer physical violence at some point in their careers (2). Most of the violence towards HCWs originates from patients and visitors. Healthcare professionals at higher risk encompass nurses, emergency room personnel, and paramedics – those directly engaged in patient care (2).

A systematic review by Liu et al. (2019) synthesized evidence on workplace violence against healthcare workers (HCWs) available up to October 2018. The review included 253 studies with a total of 331,544 participants. Findings showed that 62% of HCWs had experienced some form of workplace violence, with 43% reporting exposure to non-physical violence and 24% to physical violence in the previous year. The most common type of non-physical violence was verbal abuse (58%), followed by threats (33%) and sexual harassment (12%) (3).

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Another systematic review by Zhang et al. (2023) analyzed workplace violence against healthcare workers (HCWs) during the COVID-19 pandemic. The review included 38 studies with a total of 63,672 participants. The findings indicated high overall prevalence rates of workplace violence: 43% for any type, 9% for physical, 48% for verbal, and 26% for emotional violence. Nurses experienced more than twice the rate of physical violence compared with physicians (4). Workplace violence has a significant negative impact on HCWs because it affects their psychological and physical health, affects their job motivation, impairs their work function, compromises the quality of care, and puts healthcare provision at risk, leading to financial and social costs to employees, organizations, and society (5, 6).

Many authors have shown that both physical and non-physical violence are significantly correlated with short-term symptoms of burnout (such as emotional exhaustion, depersonalization, and inefficacy) and distressing emotions among HCWs (7). According to the findings of a 2022 systematic review, the consequences of workplace violence lead many healthcare providers to report low job satisfaction, with nearly one-third considering leaving their hospital positions (8).

Existing evidence from a recent systematic review (2023) supports the need for nurse managers to prioritize developing and implementing evidence-based strategies to mitigate violence in healthcare settings (9). These findings align with our study results, which emphasize the urgent need to establish effective institutional measures to prevent and manage workplace violence among nurses. Underreporting is a major obstacle in addressing workplace violence because it underestimates the severity of the problem and also limits prevention and intervention efforts to known incidents (5). Besides that, different forms of workplace violence are not reported equally or proportionately (9). Physical violence is likely to be more reported, while verbal violence is likely to be underreported (10, 11).

The systematic review published in 2022 found that physicians and nurses were reluctant to report violence for several reasons, including previous experience of no action being taken, fear of the consequences, and lack of management support. Additionally, they were unaware of the reporting policies and procedures (8). Available evidence on workplace violence against nurses in Croatia is limited and consists mainly of local institutional studies and student theses. Existing studies from Croatia and neighboring countries indicate high exposure of nurses to workplace violence, predominantly verbal, with patients commonly reported as perpetrators and low formal reporting rates (7, 12, 13).

Therefore, this study aimed to analyze the frequency of violence against nurses in Croatia, the psychological consequences of such violence, and the existing measures to address this problem in healthcare institutions.

Methods

Study Design

A cross-sectional study was conducted among nurses in the Republic of Croatia via an online survey from October 1 to November 4, 2023.

Participants and Recruitment

The participants were nurses employed in the Republic of Croatia. This study used a convenience sampling approach, as participation was voluntary and limited to nurses who were members of the selected Facebook group.

The participants were approached online through the Facebook group "Nurses - mutual help (diagnostic tests, scheduling, surveys)", which had 4,000 members at the time of the research. That Facebook group was designed to assist nurses by providing information on ordering diagnostic tests, scheduling patient appointments, and facilitating the completion of questionnaires and surveys for higher-education theses. The announcement text of the Facebook group post was a polite invitation to participate, emphasizing anonymity and gratitude for the time invested. The initial invitation was

sent on October 1, 2023, followed by four reminders on October 8, 15, 22, and 29. The questionnaire was closed on November 4, 2023.

Questionnaire

Participants completed an anonymous online questionnaire titled "Workplace Violence in the Health Sector Country Case Study-Questionnaire." Permission to use the questionnaire was not required. Participants did not receive any incentives, such as monetary or non-monetary rewards, for participating in this study.

The questionnaire was delivered in Croatian. For the study, the questions were translated into Croatian from English, which included the creation of two independent translations into the Croatian language (T1 and T2), synthesis of those translations (T12), two independent back translations into the original language (BT1 and BT2), and a comparison of the back translations with the original. The pre-final questionnaire was then pilot tested on a sample of 10 nursing students employed in the healthcare system who were not part of the study sample. Pilot testing was conducted to assess the questionnaire's readability and understandability. Following the pilot testing, no revisions were made to the questionnaire.

The questionnaire was conducted via the LimeSurvey platform. The questionnaire had five pages. Each page contained between 8 and 10 questions, except for the last page, which had only one question. The participants had the option to go back and correct their answers before storing them. No sensitive information was collected from the participants' devices via cookies or CAPTCHA, nor were their IP addresses recorded. Before analysis, duplicate entries with the same user ID were removed, keeping only the first entry or the entry with complete responses. Only complete responses were used in the analysis.

The part of the original questionnaire related to mobbing, racial harassment, and participants' attitudes about violence in the workplace was excluded. In the physical violence section of the questionnaire, an additional item was included to assess the frequency of physical incidents in the past 12 months. To better understand the issue of violence against nurses in Croatia, a question related to the level of education was added to the sociodemographic data.

The final version of the questionnaire consisted of 38 closed questions about sociodemographic characteristics (8 questions), physical violence (11 questions), verbal violence (9 questions), sexual violence (9 questions), and measures to solve workplace violence (1 question). The questionnaire is available in Appendix 1.

In the part of the questionnaire on physical, verbal, and sexual violence, information was collected on the frequency of violence in the last 12 months from the moment of filling out the questionnaire, whether the participants considered it a typical incident for their workplace, who the attacker was, and the response of the participants to the last incident. The participants also assessed their burden of psychological consequences after the incidents of violence with statements not at all (1), little (2), moderate (3), quite a bit (4), and extremely (5). Data were collected on the consequences for the perpetrator, the cause of the attack, and the reasons for not reporting the incident. In addition, part of the physical violence questionnaire gathered information about the time of the incident and the existence of physical injuries after the incident. Also, information was collected on existing measures to address workplace violence.

Internal consistency was evaluated for the sets of Likert-type items measuring psychological reactions to physical, verbal, and sexual violence. Although the full questionnaire included various question formats (yes/no items, checklists, and nominal indicators), only the subscales assessing psychological consequences were suitable for internal consistency testing because they shared a common underlying construct and were measured on a 5-point Likert scale. Four items were included in each subscale.

Ethics Statement

The study protocol was approved on June 15, 2023, by the Ethics Committee of The Catholic University of Croatia in Zagreb (Document number: 498-15-06-23-001). Written informed consent was obtained from all study participants. The study was conducted in accordance with the institutional Codes of Ethics. All methods were performed in accordance with the relevant guidelines and regulations.

Statistical Analyses

The data were analyzed using descriptive methods and inferential analyses to evaluate hypotheses. Categorical data were presented as percentages and frequencies. The normality of data distribution was checked with the Kolmogorov-Smirnov test. The ANOVA test was used for normally distributed data; the non-parametric Kruskal-Wallis test was used for non-normally distributed data. The differences between various groups of nurses were determined using the Chi-square test. The level of statistical significance was set at $P<0.05$. Microsoft Excel (version 2024, Microsoft Corp., Redmond, WA, USA) and IBM SPSS (Statistical package for social sciences, version 23, IBM Corp., Armonk, NY, USA) were used to analyze the data.

Results

Participant Characteristics

There were 4,000 members of the Facebook group at the time when the online survey was posted; 318 participated in this study (response rate 7.9%). Most participants (94%) were women. Regarding their education, 39% of the participants had a Bachelor of Nursing degree, while 39% completed nursing high school. More than half of the participants worked in different types of hospitals. (Table 1).

Table 1. Characteristics of the Participants (N=318)

Characteristics	N (%)*
Age	
18-28	83 (26)
28-38	83 (26)
38-48	81 (26)
48-58	59 (19)
>58	12 (3.8)
Sex	
Female	298 (94)
Male	20 (6.3)
Work experience in the health sector	
0-5	77 (24)
5-1	82 (26)
15-25	78 (25)
>25	81 (26)
Do you work in shifts	
Yes	221 (70)
No	97 (31)
The sex of the patients you most frequently work with are:	
Women	28 (8.8)
Men	4 (1.3)
Men and women	286 (90)

Continuation of Table 1.

Characteristics	N (%)*
Where do you spend most of your time (more than 50%) in your main job?	
General or County Hospital	96 (30)
Clinical Hospital Centre	67 (21)
Health Center, an institution for health care in the home	55 (17)
Clinical Hospital	38 (12)
Private health sector	22 (6.9)
Institute of Emergency Medicine	15 (4.7)
Social institutions, homes for the elderly, homes for people with intellectual disabilities	17 (5.3)
Educational institution (kindergarten, high school, college)	6 (1.9)
Institute of Public Health	2 (0.6)
The number of staff present in the same work setting with you during most (more than 50%) of your work time is:	
1-5	62 (20)
6-10	46 (15)
11-15	59 (19)
Over 15	151 (48)
Highest level of education completed	
Nursing high school	124 (39)
Bachelor of Nursing degree	125 (39)
Master of Nursing degree	68 (21)
Doctoral (PhD) degree	1 (0.3)

*Percentages may not add up to100% due to rounding.

More than half of the participants were aged below 38. The majority had more than 5 years of experience in the health sector. The majority worked in shifts, and they mostly worked with both men and women. More than half worked in a setting where more than 10 staff members were present at their workplace (Table 1).

Prevalence and Characteristics of Workplace Violence

Table 2 summarizes participants' experiences with physical, verbal, and sexual violence, including prevalence, characteristics of perpetrators, and nurses' responses to the most recent incident. As shown, exposure varied by type of violence: 21% of nurses reported physical violence, 66% reported verbal abuse, and 13% experienced sexual harassment within the past 12 months. For all three violence types, patients were the most frequent perpetrators, followed by relatives and staff members, although the distribution varied: patients accounted for 84% of physical assaults, 46% of verbal abuse, and 48% of sexual harassment cases. Staff members were reported as perpetrators mainly in verbal (21%) and sexual violence incidents (40%) (Table 2).

Responses to Violent Incidents

Participants also differed in how they responded to violence. Among physically abused nurses, the most common responses were telling the perpetrator to stop (51%), verbally defending themselves (42%), and reporting the incident to senior staff (45%). In contrast, 16% completed an official incident/accident report form. For verbal abuse, nearly half (47%) did not report the incident, and only 21% informed senior staff, consistent with broader underreporting patterns. Sexual violence elicited similar response patterns, with many choosing verbal self-defense (45%) or telling

Table 2. Characteristics of the Cases of Violence

Characteristics	Physical violence, N (%)	Verbal violence, N (%)	Sexual violence, N (%)	χ^2	P
In the last 12 months, have you been attacked/abused in your workplace?					
Yes	67 (21)	211 (66)	40 (13)	239.18	<0.001
No	251 (79)	107 (34)	278 (88		
Do you consider this to be a typical incident of violence in your workplace?					
Yes	55 (82)	195 (92)	29 (73)	14.91	<0.001
No	12 (18)	16 (7.6)	11 (27.5)		
How often have you been attacked/abused in the last 12 months?					
All the time	3 (4)	28 (8.8)	1 (2.5)	35.97	<0.001
Sometimes	47 (71)	168 (53)	24 (60)		
Once	17 (17)	15 (4.7)	15 (38)		
Please think of the last time you were attacked/abused in your place of work. Who attacked/abused you?					
Patient/client	56 (84)	97 (46)	19 (48)	48.71	<0.001
Relatives of the patient/client	4 (6)	29 (14)	2 (5)		
Staff member	3 (4)	45 (21)	16 (40)		
Management / supervisor	2 (3)	39 (19)	2 (5)		
External colleague/worker	2 (3)	1 (0.4)	1 (2.5)		
At which time did it happen?					
07.00 h - 13.00 h	26 (39)	-	-	7.57	0.06
13.00 h - 18.00 h	14 (21)				
18.00 h - 24.00 h	11 (16)				
24.00 h - 07.00 h	16 (24)				
How did you respond to the violence?					
Took no action	6 (8.9)	35 (17)	6 (15)	83.68	<0.001
Tried to pretend it never happened	4 (6)	44 (21)	9 (23)		
Told the person to stop	34 (51)	63 (30)	17 (43)		
Tried to defend myself physically	14 (21)	1 (0.5)	5 (15)		
Tried to defend myself verbally	28 (42)	99 (47)	18 (45)		
Reported it to a senior staff member	30 (45)	59 (21)	17 (43)		
I did not report the incident	11 (16.4)	42 (19.9)	4 (10)		
Told friends/family	15 (22.4)	43 (20.4)	8 (12)		
Sought counselling	3 (4.5)	14 (6.6)	1 (2.5)		
Told a colleague	24 (35.8)	74 (35.1)	14 (35)		
Completed incident/accident form	19 (28.4)	10 (5)	2 (5)		
Pursued prosecution	5 (7.5)	4 (1.9)	0 (0)		
Why didn't you report the incident?					
It was not important	4 (6)	5 (2.5)	1 (2.5)	15.36	0.12
Felt ashamed	0 (0)	1 (0.4)	0 (0)		
Felt guilty	0 (0)	1 (0.4)	0 (0)		
Afraid of negative consequences	1 (1.5)	21 (10)	1 (2.5)		
Did not know who to report to	4 (6)	30 (14.2)	1 (2.5)		
Useless	5 (8)	7 (3.3)	2 (5)		

Continuation of Table 2.

Characteristics	Physical violence, N (%)	Verbal violence, N (%)	Sexual violence, N (%)	χ^2	P
Were you injured as a result of the violent incident?					
Yes	15 (22)			20.43	<0.001
No	52 (78)	-	-		
Was any action taken to investigate the causes of the incident?					
Yes	12 (18)	29 (14)	8 (20)	2.16	0.70
No	47 (70)	147 (70)	27 (68)		
Don't know	8 (12)	35 (17)	5 (13)		
What were the consequences for the attacker?					
None	2 (17	10 (4.7)	1 (13)	20.67	0.02
Verbal warning issued	6 (50)	18 (8.4)	7 (88)		
Care discontinued	3 (25)	2 (0.9)	0 (0)		
Reported to the police	7 (58)	1 (0.45)	0 (0)		
Aggressor prosecuted	1 (8)	1 (0.45)	0 (0)		
Don't know	1 (8)	2 (0.9)	0 (0)		

a supervisor (43%), yet formal reporting remained rare (5%) (Table 2).

Reasons for Not Reporting Violent Incidents

Reasons for not reporting incidents also differed across violence types. For physical violence, the most common reasons included believing the incident was "not important" (6%) or that reporting was "useless" (8%). For verbal abuse, participants more frequently cited not knowing whom to report to (14%) or fear of negative consequences (10%). Reasons for not reporting sexual harassment were infrequent but included fear of consequences (2.5%) and perceptions that reporting would not change anything (5%) (Table 2).

No difference was found in the reporting of physical violence [χ^2=2.07<5.99 (P>0.05)] and verbal violence (χ^2=2.23; P=5.99) based on participants' level of education. A chi-square test was not performed for sexual violence because the number of those who were victims of sexual harassment was not sufficient (N=2) (Table 3).

Table 3. Reporting of Violent Incidents by Participants' Level of Education

Type of abuse	Filled out the incident/accident report form, N (%)	χ^2	P
Physically abused			
Nursing high school	10 (53)	207	0.36
Bachelor of Nursing degree	6 (32)		
Master of Nursing degree	3 (16)		
Verbally abused			
Nursing high school	2 (20)	2.23	0.33
Bachelor of Nursing degree	5 (50)		
Master of Nursing degree	3 (30)		
Sexually assaulted			
Nursing high school	1 (50)	*	*
Bachelor of Nursing degree	1 (50)		
Master of Nursing degree	0 (0)		

*Chi-square test was not performed.

Psychological Consequences of Violence

To evaluate whether the psychological consequences of workplace violence differed by years of work experience, participants rated their level of burden across four domains, including intrusive memories, avoidance, hyper-vigilance ("being super-alert"), and a sense of effortfulness, on a scale

Table 4. Presentation of Psychological Consequences of Experienced Physical, Verbal and Sexual Violence in Relation to Work Experience

Psychological consequences	<5	5-15	15-25	>25	H*	P†
Physical violence						
Repeated, disturbing memories, thoughts, or images of the attack?	3	2.5	2	2.5	1.63	0.65
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?	2	2	2.5	3	3.04	0.39
Being "super-alert" or watchful and on guard?	3	4	4	3	3.26	0.35
Feeling like everything you did was an effort?	3	3	3	3	0.25	0.97
Verbal violence						
Repeated, disturbing memories, thoughts, or images of the attack?	2.65‡	2.84‡	3.22‡	2.92‡	2.22	0.53
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?	3	3	3	3	0.20	0.98
Being "super-alert" or watchful and on guard?	3.58‡	3.39‡	3.92‡	3.63‡	2.30	0.51
Feeling like everything you did was an effort?	3.20‡	3.32‡	3.43‡	3.23‡	0.34	0.95
Sexual violence						
Repeated, disturbing memories, thoughts, or images of the attack?	2	2	3	3	1.29	0.73
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?	3	3	2.5	3	1.32	0.73
Being "super-alert" or watchful and on guard?	3	5	4	3	0.69	0.88
Feeling like everything you did was an effort?	3	3	3	3	0.84	0.84

*Kruskal–Wallis H test; †>0.05; ‡Numbers expressed as median or as average. Analyses: Chi-square test.

from 1 ("not at all") to 5 ("extremely"). As shown in Table 4, the median scores across all experience groups ranged from 2 to 4, indicating generally low to moderate psychological burden. Across all forms of violence (physical, verbal, and sexual), no statistically significant differences were observed between nurses with fewer than 5 years of experience and those with more than 25 years (all P>0.05) (Table 4).

Although the burden did not differ statistically across experience groups, certain patterns were notable. For example, hyper-vigilance ("being super-alert or watchful") consistently showed among the highest median scores across all types of violence, particularly after verbal violence (median scores 3.39–3.92), suggesting that this reaction is a common psychological response among nurses regardless of experience. In contrast, feelings of effortfulness and intrusive memories generally fell within the moderate range (median = 2 to 3), with minimal variation across groups (Table 4).

Workplace Measures to Address Violence

Regarding workplace measures to address workplace violence, most participants (N=75; 24%) reported security measures such as guards, alarms, and portable phones. This was followed by patient protocols, including control and restraint procedures, transport, medication, and access to information, which were mentioned by 66 participants (21%). Almost half (N=154, 48%) of participants reported that none of the mentioned measures were implemented at their workplace (Table 5).

Internal Consistency

Internal consistency was assessed for the psychological reaction scales related to physical violence, verbal abuse, and sexual harassment. Cronbach's alpha indicated acceptable reliability across all three scales: α=0.75 for reactions following physical violence, α=0.77 for reactions following verbal abuse, and α=0.77 for reactions following sexual harassment.

Table 5. Presentation of Measures to Solve the Problem of Violence in the Workplace

What measures exist to deal with violence in your workplace?	N (%)
Security measures (e.g., guards, alarms, portable telephones)	75 (24)
Patient protocols (e.g., control and restraint procedures, transport, medication, activities programming, access to information)	66 (21)
Patient screening (to record and be aware of previous aggressive behaviour)	55 (17)
Promotion of a healthy environment	46 (15)
Training (e.g., workplace violence, coping strategies, communication skills, conflict resolution, self-defence)	33 (10)
Changed shifts or rotas (i.e., working times)	27 (8.5)
Restrict public access	26 (8.2)
Check-in procedures for staff (especially for home care)	19 (6)
Increased staff numbers	14 (4.4)
Reduced periods of working alone	14 (4.4)
Restrict exchange of money at the workplace (e.g. patient fees)	6 (1.9)
None of these	154 (49)

Discussion

The results of the study showed that most participating nurses reported experiencing workplace violence in the past 12 months, with verbal violence being the most common. Psychological burden was generally moderate and did not differ by education level or years of work experience. Nearly half of respondents reported the absence of workplace measures to address violence, with security-related interventions being the most frequently mentioned where measures existed. This study complements existing research by providing context-specific data from Croatia and by examining reporting behaviors, psychological consequences, and the workplace. These findings reflect the experiences of nurses who participated in this survey and should not be interpreted as definitive evidence of nationwide prevalence or institutional practices. measures within a single sample.

Characteristics of Violent Incidents

Our study found that verbal abuse was the most common form of violence in the workplace, with patients being the primary perpetrators of physical, verbal, and sexual violence against nurses. Staff and supervisors were also frequently responsible for verbal abuse. Very few studies on this topic among nurses from Croatia have been published. A study conducted in 2017 in Osijek, Croatia, examined workplace violence against nurses at the Clinical Hospital Center Osijek, including 20% of the staff. The study was focused on exploring the exposure to maltreatment and violence at the workplace over the past six months. According to the results, 40% of the 275 participants reported experiencing workplace violence. Among those, 44% experienced violence by supervisors, 39% by colleagues, and 26% by patients and students (12).

A study conducted in 2020 on 328 nurses in Croatia revealed that only 7% of participants had not experienced any form of violence at the workplace. However, this data does not pertain solely to the past 12 months, as in our study. The most common form of violence reported was verbal abuse, with only 4% (N=13) of respondents stating they had no experience with it, while 83% (N=271) reported experiencing verbal abuse multiple times. Following verbal abuse, physical violence was reported by 51% and sexual violence by 27% of respondents (14). Similar to the results of our study, patients were most frequently identified as the perpetrators of physical (86%) and verbal violence (77%). However, there was a difference in the perpetrators of sexual violence, with the majority (60%) being physicians (14).

In our study, the survey did not offer "physicians" as a response option for perpetrators of violence; instead, "staff" was provided. Among

participants who experienced sexual violence (N=40), almost half reported that it was perpetrated by patients, and 16 (40%) reported experiencing sexual violence from "staff."

A study conducted in the Czech Republic and Slovakia in 2020 found that in the past 12 months, 18% of nurses from both Slovakia and the Czech Republic experienced physical violence. Verbal abuse was the most common form of violence in both countries, similar to the results of our study; it was reported by 48% of respondents in Slovakia and 61% in the Czech Republic. The results from the Czech Republic are closer to the results of this study. In both countries, patients were most frequently identified as the perpetrators of both forms of violence, just as in this study (13).

Psychological Consequences of Violence

The most common psychological consequences of all types of violence at the workplace among our participants were being "super-alert" or watchful and on guard. Several studies have found similar psychological consequences of workplace violence, including the experience of being "super-alert" or watchful and on guard, which aligns with our findings. For instance, research conducted among healthcare workers in the Greater Accra region of Ghana revealed that a significant proportion of those who experienced workplace violence, whether physical, verbal, or sexual, reported becoming more vigilant and watchful as a consequence (15). A systematic review of prospective and longitudinal studies on workplace violence, particularly in healthcare and human service industries, found consistent evidence of psychological consequences like heightened alertness or hyper-vigilance among workers exposed to violence. This state of being "super-alert" was frequently observed as a response to both physical and psychological violence, which reinforces the findings from your study (16).

Furthermore, in our study, there was no significant difference in the intensity of psychological consequences between respondents with more or less than five years of work experience in the context of any form of violence. This indicates that the duration of work experience does not significantly affect the psychological consequences of violent incidents in our sample.

Results from a 2020 study in Croatia showed that, of 298 respondents, 50% reported being sometimes concerned about workplace safety, and only 7.9% sought psychological help. Additionally, 31% of respondents reported avoiding their attacker at work, while 36% of respondents indicated that their experience with violence did not affect their work (14).

The results of the study conducted on Slovak and Czech nurses showed that a statistically significant difference was found in the intensity of psychological responses to physical and verbal violence between nurses in those two countries. In Slovakia, most respondents (47%) reported being significantly bothered by the feeling of "hyper-vigilance" after a violent incident, while in the Czech Republic, 35% reported being significantly affected by it (13). There is evidence that the most common consequences of workplace violence include being "superalert" or watchful and on guard (17), which is consistent with the results of our study.

Reporting Violence at the Workplace

This study showed that reporting violence in the workplace was low and did not find a significant difference in reporting violent incidents based on the level of education. Respondents reported incidents equally, regardless of their education level. They did not describe cases of non-reporting of sexual violence due to feelings of shame. However, this may not reflect reality, and respondents may have provided socially desirable answers. Notably, among 40 nurses who reported experiencing sexual violence in our study, 40% experienced it from "staff," and 5% reported experiencing sexual violence from superiors. These numbers suggest that such cases might go unreported to avoid stigmatization and additional workplace discomfort.

A study in Slovenia showed that workplace violence against nurses was common, while formal reporting rates were low, particularly for sexual

violence, mainly due to perceptions that reporting would be ineffective and fear of job-related consequences (18). A retrospective cross-sectional study conducted among registered nurses in Poland, the Czech Republic, the Slovak Republic, Turkey, and Spain found that about half of the study group did not report workplace violence because they believed it was useless or not important (17).

According to the systematic review aimed to investigate nurses' reasons and rationale related to the underreporting of violence that occurs in the workplace, the most prominent factors included nurses' fear of consequences after reporting, nurses' perceptions, and their lack of knowledge about the reporting process (9). Five of the 19 studies used the term "part of the job", while other studies described this synonymously as "common to their care area" or "desensitized to violent patients" (9).

Furthermore, a scoping review aimed to describe and synthesize the scientific literature on nurses' formal reporting of workplace violence, which included 49 studies, revealed four key issues related to workplace violence reporting. These issues were: (1) reporting rates are generally low, with oral reports being the most common method; (2) nurses often express dissatisfaction with how their reports are handled by their organizations; (3) the reasons influencing reporting are varied and complex; and (4) few studies have suggested formal measures to encourage reporting (19).

Measures for Addressing Workplace Violence

In our study, almost half of the participants reported the non-existence of preventive measures against workplace violence at their jobs. Where available, the most common measures mentioned were security measures such as guards and alarms, followed by protocols for patient restraint and control, medication and transportation controls, and other related measures.

According to the results of a systematic review conducted with the aim to explore the topics focused on and to detect new evidence about approaching the issue of workplace violence toward HCWs in Emergency departments, an effective strategy for managing workplace violence should emphasize training programs that focus on developing strong healthcare worker-patient relationships, enhancing communication skills among workers, ensuring precise reporting of violent incidents, and improving the work environment with active management support and employee participation in workplace violence prevention initiatives (7). Accordingly, a study conducted in Croatia in 2020 highlighted that 65% of nurses indicated that additional education would help in better handling violent individuals (7). The results of our study indicate that only 10.4% of participants reported that one of the measures in place to address workplace violence was training, which included topics such as workplace violence, coping strategies, communication skills, conflict resolution, and self-defense.

The study conducted in Germany in 2018, which included 81 healthcare institutions and 1,984 healthcare workers, found that although many healthcare institutions have introduced preventive measures against workplace violence, comprehensive risk assessment and systematic prevention remain inconsistent, and increased awareness may contribute to higher reporting rates (20) 81 different healthcare facilities and 1984 employees participated. The questionnaire encompassed socio-demographic details, the frequency of physical violence and verbal abuse, consequences of violence and the stress of employees. In the previous twelve months, 94.1% of the employees in the survey had experienced verbal abuse and 69.8% had experienced physical aggression. Acts of aggression were most commonly encountered in hospitals and residential facilities for the disabled. One third of the employees felt under high levels of stress as a result of the incidents. If the workplace prepares effectively, however, this reduces the perceived stress odds ratio (OR.

According to a study of 35 national nurses' associations across Europe, workplace violence against nurses reflects broader systemic and legislative gaps, highlighting the need for stronger institutional and policy-level action (21). Compared

with international findings, our results suggest that Croatian nurses report fewer structured preventive measures, indicating that implementation gaps may be more pronounced in this context.

Limitations of the Study

A limitation of the study is the relatively small sample size. According to data from the Croatian Institute of Public Health, as of May 10, 2023, there were 32,440 nurses employed in the healthcare sector in the Republic of Croatia (22). Therefore, the study involved about 1% of the nurses in Croatia. However, the data collection method via a Facebook group also presents certain limitations. For example, not all nurses in Croatia are members of that Facebook group. The group has 4,000 members, so the response rate among group members was 7.9%. Although the survey was posted in the group five times, including the initial invitation and four reminders, it is possible that not all group members saw the survey. It is also possible that nurses are tired of frequent requests to complete online surveys, resulting in a low response rate within the group. Because the study relied on a convenience sample recruited via a social media group, the results may be subject to selection bias and may not reflect the experiences of all nurses employed in Croatia. Additionally, there was a dispersion of respondents according to the types of violence they experienced; for instance, relatively few respondents described sexual violence. Furthermore, a large portion of respondents were women, leading to insufficient data to analyze violence against men. However, women make up the majority of the nursing population in Croatia (86%), so the gender distribution of respondents in this study aligns with that of the population in Croatia.

Ideas for Future Research

Future studies should include a larger and more diverse sample to enable regional and institutional comparisons of workplace violence among nurses in Croatia. Expanding research to include other healthcare professionals could help identify interprofessional differences in both exposure to and response to workplace violence. Additionally, further investigation is needed to understand barriers to reporting violent incidents and to inform the development of targeted interventions and support mechanisms for affected staff.

Conclusion

This study indicates that workplace violence against nurses is a common and underreported problem among the nurses included in this sample, most often perpetrated by patients. The reported absence of preventive measures in many participants' workplaces highlights potential gaps in institutional responses and suggests the need for further evaluation and improvement of safety policies. Previous evidence indicates that workplace violence may be mitigated through staff training, clear reporting pathways, organizational support, routine risk assessment, and appropriate security measures. Strengthening these approaches may help improve prevention, reporting, and management of violent incidents in healthcare settings. Implementing evidence-based prevention strategies is essential to create safer healthcare environments and enhance nurses' well-being.

What Is Already Known about This Topic:

Workplace violence against nurses is a well-documented global problem that negatively affects healthcare professionals' safety, mental health, and job satisfaction. Numerous studies worldwide have shown that nurses are among the occupational groups most exposed to verbal, physical, and sexual violence in the workplace. Such incidents contribute to increased stress, burnout, and staff turnover, and they can compromise the quality of patient care. International organizations, including the World Health Organization (WHO) and the International Labour Organization (ILO), have emphasized the need for effective prevention and reporting mechanisms to reduce workplace violence in healthcare. However, most existing research has been conducted in high-income countries, and data from Central and Eastern Europe remain limited, particularly regarding Croatia (7, 12, 13).

What This Study Adds:

Due to our knowledge, this study provides the first comprehensive national insight into the prevalence, types, and consequences of workplace violence against nurses in Croatia. It reveals that 70% of nurses experienced some form of workplace violence in the past year, predominantly verbal abuse, and nearly half reported the absence of institutional mea-

sures to address it. The findings highlight significant gaps in workplace safety and underscore the urgent need for systemic interventions and policies. By providing localized data, the study contributes to global research and supports evidence-based action to protect healthcare professionals in Croatia.

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Appendix 1. Questionnaire Used in the Study

In this questionnaire, workplace violence refers to incidents in which staff are abused, threatened, or assaulted in situations related to their work. This includes incidents occurring while commuting to and from work and those that involve an explicit or implicit threat to personal safety, well-being, or health.

A. SOCIODEMOGRAPHIC CHARACTERISTICS

1. Age:
   18-28
   28-38
   38-48
   48-58
   >58

2. Sex:
   Female
   Male

3. Work experience in the health sector:
   0-5
   5-15
   15-25
   >25

4. Do you work in shifts?
   Yes
   No

5. The sex of the patients you most frequently work with are:
   Women
   Men
   Men and women

6. Where do you spend most of your time (more than 50%) in your main job?
   General or County Hospital
   Clinical Hospital Centre
   Health Center, an institution for health care in the home
   Clinical Hospital
   Private health sector
   Institute of Emergency Medicine
   Social institutions, homes for the elderly, homes for people with intellectual disabilities
   Educational institution (kindergarten, high school, college)
   Institute of Public Health

7. The number of staff present in the same work setting with you during most (more than 50%) of your work time is:
   1-5
   6-10
   11-15
   Over 15

8. Completed degree of education:
   Nursing high school
   Bachelor of Nursing degree
   Master of Nursing degree
   Doctoral (PhD) degree

B. PHYSICAL VIOLENCE

9. In the last 12 months, have you been physically attacked in your workplace?
   Yes
   No

10. Do you consider this to be a typical incident of violence in your workplace?
    Yes
    No

11. How often have you been physically attacked in the last 12 months?
    All the time
    Sometimes
    Once
12. Please think of the last time you were physically attacked in your place of work. Who attacked you?
    Patient/client
    Relatives of patient/client
    Staff member
    Management / supervisor
    External colleague/worker

13. At which time did it happen?
    07.00 h. - 13.00 h.
    13.00 h. - 18.00 h.
    18.00 h. - 24.00 h.
    24.00 h. - 07.00 h.

14. How did you respond to the violence?
    Took no action
    Tried to pretend it never happened
    Told the person to stop
    Tried to defend myself physically
    Tried to defend myself verbally

Reported it to a senior staff member
I did not report the incident
Told friends/family
Sought counselling
Told a colleague
Completed incident/accident form
Pursued prosecution

15. Why didn't you report the incident?
It was not important
Felt ashamed
Felt guilty
Afraid of negative consequences
Did not know who to report to
Useless

16. Were you injured as a result of the violent incident?
Yes
No

17. Was any action taken to investigate the causes of the incident?
Yes
No
Don't know

18. What were the consequences for the attacker?
None
Verbal warning issued
Care discontinued
Reported to police
Aggressor prosecuted
Don't know

19. Listed below are a list of problems and complaints that people sometimes have in response to stressful life experiences like the event that you suffered. *For each item, please indicate how bothered you have been by these experiences since you were attacked. Please tick one option per question.*

Since you were attacked, how bothered have you been by:	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
Repeated, disturbing memories, thoughts, or images of the attack?					
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?					
Being "super-alert" or watchful and on guard?					
Feeling like everything you did was an effort?					

C. VERBAL ABUSE

20. In the last 12 months, have you been verbally abused in your workplace?
    Yes
    No

21. Do you consider this to be a typical incident of violence in your workplace?
    Yes
    No

22. How often have you been verbally abused in the last 12 months?
    All the time
    Sometimes
    Once

23. Please think of the last time you were verbally abused in your place of work. Who abused you?
    Patient/client
    Relatives of patient/client
    Staff member
    Management / supervisor
    External colleague/worker

24. How did you respond to the violence?
    Took no action
    Tried to pretend it never happened
    Told the person to stop
    Tried to defend myself physically
    Tried to defend myself verbally
    Reported it to a senior staff member
    I did not report the incident
    Told friends/family
    Sought counselling
    Told a colleague
    Completed incident/accident form
    Pursued prosecution

25. Why didn't you report the incident?
    It was not important
    Felt ashamed
    Felt guilty
    Afraid of negative consequences
    Did not know who to report to
    Useless

26. Was any action taken to investigate the causes of the incident?
    Yes
    No
    Don't know

27. What were the consequences for the attacker?
    None
    Verbal warning issued
    Care discontinued
    Reported to police
    Aggressor prosecuted
    Don't know

28. Listed below are a list of problems and complaints that people sometimes have in response to stressful life experiences like the event that you suffered. *For each item, please indicate how bothered you have been by these experiences since you were abused. Please tick one option per question.*

Since you were abused, how bothered have you been by:	Not at All (1)	A Little Bit(2)	Moderately (3)	Quite a Bit (4)	Extremely (5)
Repeated, disturbing memories, thoughts, or images of the attack?					
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?					
Being "super-alert" or watchful and on guard?					
Feeling like everything you did was an effort?					

D. SEXUAL HARASSMENT

29. In the last 12 months, have you been sexually harassed in your workplace?
    Yes
    No

30. Do you consider this to be a typical incident of violence in your workplace?
    Yes
    No

31. How often have you been sexually harassed in the last 12 months?
    All the time
    Sometimes
    Once

32. Please think of the last time you were sexually harassed in your place of work. Who harrased you?
    Patient/client
    Relatives of patient/client
    Staff member
    Management / supervisor
    External colleague/worker

33. How did you respond to the violence?
    Took no action
    Tried to pretend it never happened

Told the person to stop
Tried to defend myself physically
Tried to defend myself verbally
Reported it to a senior staff member
I did not report the incident
Told friends/family
Sought counselling
Told a colleague
Completed incident/accident form
Pursued prosecution

34. Why didn't you report the incident?
It was not important
Felt ashamed
Felt guilty
Afraid of negative consequences
Did not know who to report to
Useless

35. Was any action taken to investigate the causes of the incident?
Yes
No
Don't know

36. What were the consequences for the attacker?
None
Verbal warning issued
Care discontinued
Reported to police
Aggressor prosecuted
Don't know

37. Listed below are a list of problems and complaints that people sometimes have in response to stressful life experiences like the event that you suffered. *For each item, please indicate how bothered you have been by these experiences since you were abused. Please tick one option per question.*

Since you were harrased, how bothered have you been by:	Not at all (1)	A Little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
Repeated, disturbing memories, thoughts, or images of the attack?					
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?					
Being "super-alert" or watchful and on guard?					
Feeling like everything you did was an effort?					

E. HEALTH SECTOR EMPLOYER

38. What measures to deal with workplace violence exist in your workplace?
Security measures (e.g. guards, alarms, portable telephones)
Restrict public access
Patient screening (to record and be aware of previous aggressive behaviour)
Patient protocols (e.g. control and restraint procedures, transport, medication, activities programming, access to information)
Restrict exchange of money at the workplace (e.g. patient fees)
Increased staff numbers
Check-in procedures for staff (especially for home care)
Changed shifts or rotas (i.e. working times)
Reduced periods of working alone
Training (e.g. workplace violence, coping strategies, communication skills, conflict resolution, self-defence)
Promotion of healthy environment
None of these

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Gastrocolic Trunk: Anatomical Variations and Surgical Significance

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Abstract

Objective. This review aims to summarize the Henle trunk configurations and tributary patterns presented in cadaveric, intraoperative, and imaging studies. **Background.** The Henle gastrocolic trunk is a highly variable venous structure formed by the confluence of the gastric, colic, and pancreatic veins. It has notable surgical importance, particularly during laparoscopic procedures, such as right colectomy and pancreaticoduodenectomy. **Methods.** A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted using the PubMed/MEDLINE and Google Scholar databases. **Discussion.** Twenty-one publications comprising 2,454 cases were analyzed to classify Henle trunk configurations and tributary patterns. The trunk was identified in 92.5% of the cases, with the gastropancreatocolic (GPC) type being the most prevalent (73.1%). A total of 38 unique venous confluences were recorded, highlighting the considerable anatomical complexity and variability of the trunk. The Henle gastrocolic trunk is a common anatomical structure with significant heterogeneity in its venous configurations. The GPC type, most frequently formed by the confluence of the right gastroepiploic vein, the anterior superior pancreaticoduodenal vein, and either the right colic vein or the superior right colic vein, predominates across cadaveric, intraoperative, and imaging studies. Understanding this variability is crucial for ensuring safe dissection during pancreatic and colorectal resections. **Conclusion.** Comprehensive knowledge of the Henle trunk anatomy and its variations enhances operative planning, minimizes the risk of vascular injury, and supports safer and more efficient minimally invasive abdominal surgery.

Key Words: Henle Gastrocolic Trunk ▪ Venous Anatomy ▪ Colorectal Surgery ▪ Pancreaticoduodenectomy.

Introduction

Anatomical variation is not an exception but the rule and represents a foundational principle of human biology, particularly evident in the venous anatomy of the gastrointestinal tract (1). In 1868, Jacob Henle characterized a venous variation, the venous trunk of Henle (also known as the Henle gastrocolic trunk), as a blood vessel that a) consists of two branches, the right gastroepiploic vein (RGEV) and the right colic vein (RCV), and b) drains into the superior mesenteric vein (SMV) at the lower edge of the pancreas (2). In 1912, Decomps et al. discovered a pancreatic tributary associated with the Henle trunk, which they referred to as either the anterior superior pancreaticoduodenal vein (ASPDV) or the anterior inferior pancreaticoduodenal vein (AIPDV) (3). This finding completed the definition of the Henle trunk as a tripod anatomical structure. Given the growing importance of the Henle trunk in surgical procedures, further research has identified new tributaries and various possible confluences of these veins (4-7).

In recent years, laparoscopic techniques for colon cancer have progressed notably, with the adoption of complete mesocolic excision (CME) and central vascular ligation (CVL) during right colectomy rising significantly (8, 9). Such procedures can result in complications, such as severe bleeding; thus, successful outcomes depend on a precise understanding of essential anatomical

structures, such as the trunk of Henle (10). It is crucial to identify the veins draining into the Henle trunk when performing a pancreaticoduodenectomy (11). Dissection at the trunk of Henle provides access to the infrapancreatic section of the superior mesenteric vein (SMV), which is essential during the Whipple procedure (12). Consequently, numerous research teams have investigated the anatomical structure of the Henle trunk using intraoperative and advanced imaging techniques in recent years (13-15).

This study aimed to gather and examine both historical and contemporary scientific data to accurately describe the morphological characteristics of the Henle trunk.

Methods

This systematic review was conducted following the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16, 17). The review protocol was submitted to the Institutional Review Board of the Department of Anatomy at the National and Kapodistrian University of Athens, Greece, and is accessible upon request. A literature search across the PubMed/MEDLINE and Google Scholar databases was conducted to assess the anatomy of the Henle trunk using the search terms: "Henle gastrocolic trunk," "trunk of Henle," "Henle's gastrocolic trunk," "gastrocolic trunk," "gastrocolic vein," "gastrocolic trunk of Henle," "gastrocolic veins," "gastro-colic venous trunk," as well as the Boolean operators "AND" and "OR." All co-authors approved the study protocol. Language restrictions were applied, considering only articles published in English, French, or German. Two investigators (GS and DC) independently conducted literature searches and extracted data from all eligible studies. Review articles were excluded, whereas all prospective and retrospective studies, along with case reports, were included in this systematic review.

Furthermore, all references were reviewed to identify relevant reviews, and suitable articles were retrieved from this search for potentially relevant conference abstracts. The titles of interest were further examined through their abstracts. Eligible articles were identified from the inception of the databases until November 2025. Ultimately, 21 studies were included in the analysis (4-6, 10, 11, 13-15, 18-30), encompassing cadaveric, intraoperative, and imaging studies involving a total of 2,454 subjects. The studies were categorized based on their methodological approaches for the stratified analysis. To evaluate the distribution of venous confluences, the frequency of each identified configuration of the Henle trunk was calculated. A chi-square test was conducted to determine whether the distribution of the 38 identified venous confluences significantly deviated from a uniform distribution, with statistical significance set at $P<0.001$.

Results

Article Selection

The search strategy retrieved 41 articles that were considered for full-text evaluation. Twenty-one studies were deemed eligible and were included in the analytic cohort. Overall, studies encompassing a total of 2454 patients were included in this systematic review. The search strategy is illustrated in Figure 1.

Analysis of Henle Trunk Tributaries

The Henle trunk presents high variability, consisting of many different combinations of venous tributaries. The literature presents distinct views concerning the definition of the Henle trunk. In this study, the Henle trunk was defined as any combination of gastric, colic, and pancreatic venous tributaries draining on the right border of the superior mesenteric vein below the pancreas. To organize our findings, the studies were grouped into cadaveric, intraoperative, and imaging studies.

Cadaveric Studies

Seven studies, including 296 cases, described Henle vessel variations using cadaveric examinations (Table 1).

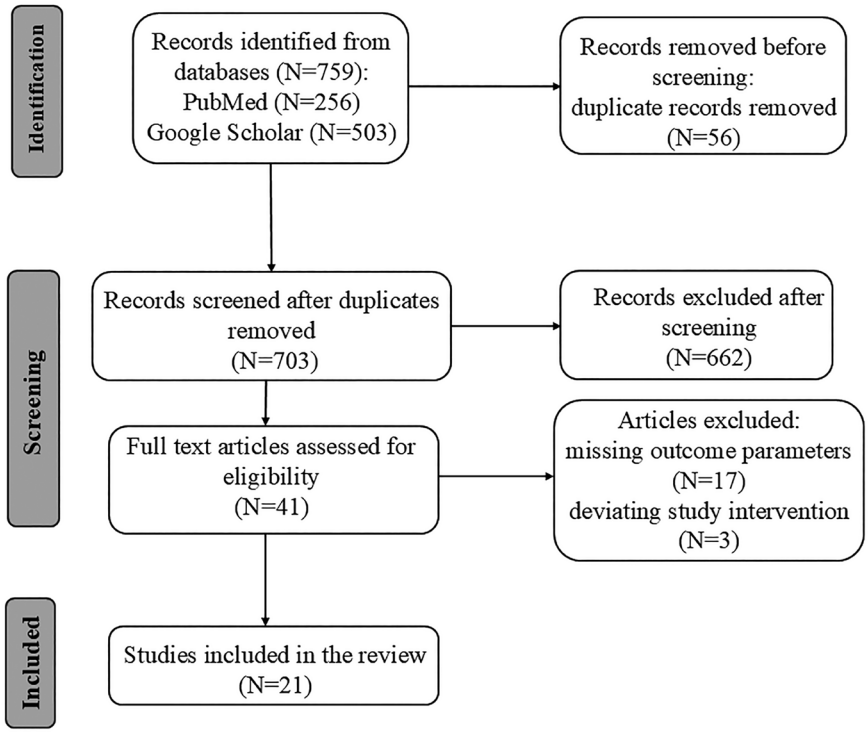

Figure 1. PRISMA flow diagram of study selection.

Table 1. Henle Trunk Forming Veins

Study Type	Author	Year	Cases	Frequency	Confluences	Number of Subjects
Cadaveric	Zhang et al. (4)	1994	54	51	RGEV + ASPDV + SRCV	18
					RGEV + ASPDV + SRCV + antral branch of the right gastroepiploic v.	5
					RGEV + ASPDV + SRCV + AIPDV	3
					RGEV + ASPDV + SRCV + middle right colic vein	1
					RGEV + ASPDV + SRCV + retropyloric v.	1
					RGEV + ASPDV	13
					RGEV + ASPDV + AIPDV	5
					RGEV + AIPDV	1
					RGEV + SRCV	4
	Yamaguchi et al. (5)	2002	58	41	RGEV + ASPDV + MCV	7
					RGEV + ASPDV+ aMCV	23
					RGEV + ASPDV + RCV	11
	Ignjatovic et al. (19)	2004	10	10	RGEV + ASPDV+MCV	1
					RGEV + ASPDV	9
	Jin et al. (20)	2006	9	9	RGEV + ASPDV + SRCV + RCV	4
					RGEV + ASPDV + SRVC	3
					RGEV + ASPDV + SRCV + RCV + MCV	1
					RGEV + ASPDV	1
	Ignjatovic et al. (18)	2010	42	34	RGEV + ASPDV + SRCV	25
					RGEV + SRCV	9

Continuation of Table 1.

Study Type	Author	Year	Cases	Frequency	Confluences	Number of Subjects
Cadaveric	Açar et al. (21)	2014	12	12	RGEV + ASPDV + SRCV	8
					RGEV + ASPDV + SRCV + MCV	2
					RGEV + ASPDV + SRCV + RCV	1
					RGEV + ASPDV	1
	Kuzu et al. (6)	2017	111	111	RGEV + ASPDV + RCV	46
					RGEV + ASPDV + SRCV + RCV	14
					RGEV + ASPDV + SRCV	12
					RGEV + ASPDV + RCV + MCV	4
					RGEV + ASPDV + RCV + ICV	3
					RGEV + ASPDV + MCV	2
					RGEV + ASPDV + ICV	2
					RGEV + ASPDV + SRCV + RCV + MCV	2
					RGEV + ASPDV + SRCV + RCV + ICV	2
					RGEV + ASPDV	24
Intraoperative	Lange et al. (22)	2000	37	33	RGEV + ASPDV + SRCV	14
					RGEV + ASPDV	16
					RGEV + SRCV	3
	Lee et al. (10)	2016	116	116	RGEV + ASPDV + SRCV	63
					RGEV + ASPDV + SRCV + aSRCV	29
					RGEV + ASPDV	19
					ASPDV + SRCV	5
	Alsabilah et al. (23)	2017	70	55	RGEV+ ASPDV + RCV	10
					RGEV + ASPDV + aMCV	5
					RGEV + ASPDV + RCV + MCV	2
					RGEV + ASPDV + MCV	2
					RGEV + ASPDV	36
	Wu et al. (24)	2019	60	53	RGEV + ASPDV + RCV	14
					RGEV + ASPDV + RCV + MCV	10
					RGEV + ASPDV + MCV	4
					RGEV + ASPDV	5
					RGEV + RCV	13
					RGEV + MCV	1
					RGEV + RCV + MCV	5
					RGEV + double RCV	1
	He et al. (13)	2022	583	567	RGEV + ASPDV + RCV	253
					RGEV + ASPDV + sRCV	32
					RGEV + ASPDV + MCV	14
					RGEV + ASPDV + aMCV	4
					RGEV + ASPDV + RCV + sRCV	64
					RGEV + ASPDV + RCV + MCV	55
					RGEV + ASPDV + RCV + aMCV	26
					RGEV + ASPDV + sRCV + MCV	4
					RGEV + ASPDV + sRCV + aMCV	2
					RGEV + ASPDV + RCV + ICV	2
					RGEV + ASPDV + RCV + SRCV + MCV	17
					RGEV + ASPDV + RCV + SRCV + aMCV	11
					RGEV + ASPDV + RCV + MCV +aMCV	2
					RGEV + ASPDV + RCV + SRCV + aSRCV	1
					RGEV + ASPDV	80

Continuation of Table 1.

Study Type	Author	Year	Cases	Frequency	Confluences	Number of Subjects
Intraoperative	Ghimire et al. (30)	2024	49	45	RGEV + ASPDV + SRCV	21
					RGEV + ASPDV + SRCV + RCV	11
					RGEV + ASPDV + SRCV + RCV + MCV	1
					RGEV + ASPDV	12
Imaging	Sakaguchi et al. (25)	2010	102	79	RGEV + SRCV	42
					RGEV + SRCV + RCV	15
					RGEV + SRCV + MCV	10
					RGEV + SRCV + RCV + MCV	9
					RGEV + MCV	2
					RGEV + RCV	1
	Ogino et al. (26)	2014	81	71	RGEV + ASPDV + RCV	29
					RGEV + ASPDV + RCV + MCV	22
					RGEV + ASPDV + RCV + SRCV	14
					RGEV + ASPDV + SRCV + RCV + MCV	3
					RGEV + ASPDV + RCV + MCV + ICV	2
					RGEV + ASPDV + ICV	1
	Miyazawa et al. (11)	2015	120	100	RGEV + ASPDV + SRCV	71
					RGEV + ASPDV + SRCV + MCV	13
					RGEV + ASPDV + SRCV + RCV	7
					RGEV + ASPDV	7
	Gao et al. (27)	2018	120	102	RGEV + ASPDV + SRCV	32
					RGEV + ASPDV + RCV	17
					RGEV + ASPDV + SRCV + RCV	12
					RGEV + ASPDV + SRCV + RCV + MCV	5
					RGEV + ASPDV + MCV	3
					RGEV + SRCV	12
					RGEV + RCV	8
					RGEV + SRCV + RCV	7
					RGEV + SRCV + MCV	4
					RGEV + RCV + MCV	2
	Gu et al. (28)	2021	96	78	RGEV + ASPDV + RCV	36
					RGEV + ASPDV + SRCV + RCV	22
					RGEV + ASPDV + SRCV + MCV	12
					RGEV + ASPDV + MCV	2
					RGEV + ASPDV	6
	Grytsenko et al. (29)	2022	103	83	RGEV + ASPDV + RCV	55
					RGEV + ASPDV + MCV + aMCV	12
					RGEV + MCV	15
					RGEV + RCV + ICV	1
	Yu et al. (14)	2023	418	418	RGEV + ASPDV + SRCV	158
					RGEV + ASPDV + RCV + SRCV	66
					RGEV + ASPDV + RCV	20
					RGEV + ASPDV	122
	Zhao et al. (15)	2024	203	203	RGEV + ASPDV + SRCV	114
					RGEV + ASPDV + SRCV + RCV	24
					RGEV + ASPDV + SRCV + MCV	23
					RGEV + ASPDV + MCV	5
					RGEV + ASPDV + SRCV + ICV	3
					RGEV + ASPDV + SRCV + MCV + ICV	1
					RGEV + ASPDV	33

The occurrence of the Henle trunk varied from 71% (5) to 100% in three of the seven studies (6, 18, 21). The gastro-pancreato-colic (GPC) type of the Henle trunk was the most frequent type in most studies, reaching 100% in the report by Kuzu et al. (6). The gastro-pancreatic trunk (GP) was more common in only two studies (19, 23). The GPC Henle trunk was formed by the RGEV, ASPDV tributaries, and a colic vein. The colic vein was either SRCV (4, 18, 21) or RCV (6) in most cases. However, in the study by Yamaguchi et al. (5), the accessory MCV (aMCV) appeared as the most common colic vein. In some studies, a combination of more than one colic vein contributed to the Henle trunk (4, 20, 21). In rare cases, the ileocolic vein (ICV) was also described as a tributary of the trunk (6). With respect to the pancreatic veins, the anterior superior pancreaticoduodenal vein is the pancreatic tributary present in almost all cases, whereas the anterior inferior pancreaticoduodenal vein (AIPDV), though rarely encountered, was also observed as a feature of the Henle trunk (4).

Intraoperative Studies

Intraoperative studies (Table 1) represent the most accurate method for identifying variations of the trunk of Henle. In recent years, many reports comprising a considerable number of cases have contributed to the clarification of the anatomy of the trunk (13, 24). The six intraoperative studies presented in Table 1 comprise 915 cases, of which 692 were reported in the last six years. The Henle trunk is present in a high percentage of intraoperative studies, starting from 79% (23) and reaching 100% (10). The gastro-pancreato-colic (GPC) type dominates the Henle trunk in these studies (10, 13, 24), in accordance with the cadaveric analysis reported above. The only exception is the study by Alsabilah et al. (23), where the gastro-pancreatic (GP) type occurs more frequently than the GPC type. RGEV and ASPDV are gastric and pancreatic tributaries, respectively, that are always observed in the GPC trunk during surgery. In most cases, the colic vein is the SRCV (10) or the RCV (13), appearing separately or together. The MCV is also found in more recent analyses (13, 25, 29), mostly in combination with the SRCV and RCV, and rarely alone (24, 25). ICV has also been reported in a limited number of studies (13) in combination with other colic veins.

Imaging Studies

The preoperative evaluation of the complex and diverse trunk of Henle before laparoscopic surgery is extremely important since it helps avoid intraoperative bleeding and serves as an anatomical marker due to the particularity of its location (14). Modern 3D imaging techniques are noninvasive and reliable, offering great assistance to surgeons. Imaging studies of the Henle trunk comprise 8 studies and 1243 cases (Table 1), in which the percentage of the trunk varies from 75% (26) to 100% (14, 15). Consistent with the cadaveric and intraoperative studies mentioned above, the GPC type of the trunk is the most abundant, with the exception of the study by Sakaguchi et al. (25), where, surprisingly, the ASPDV vein is completely absent. The SRCV appears again more frequently in this Henle type (11, 14, 15, 27), along with the RCV (26, 28, 29). Rare colic tributaries, such as the ICV or aMCV, have also been reported in imaging studies (15, 26, 29). The ASPDV monopolizes the pancreatic tributaries.

Henle Trunk Tributaries Summary

Overall, the Henle trunk is present in percentages ranging from 71% to 100% of all cases studied using the three different approaches mentioned above, whereas the pooled prevalence of the trunk is 92.54%. The GPC is the main type of the trunk, corresponding to 73.09%, followed by the GP at 17.17% and GC at 9.51%. The PC type is very rare, accounting for only 0.22% of cases. The SRCV, RCV, and the combination of the two account for approximately 57.29% of the 73.09% of the GPC Henle trunk and 7.31% of the 9.51% of the GC trunk. The two veins also appear in combination with other colic veins, thereby increasing their total percentage. MCV is also often present in the GPC type of the trunk, representing alone

or in combination with other colic veins, 9.64% of the GPC type. MCV is also a tributary of the GC Henle type. The colic veins, aMCV and ICV, are rarely part of the trunk. ASPDV is the prevalent vein of the pancreatic tributaries since only Zhang (4) refers to another pancreatic vein, the AIPDV.

Analysis of Venous Trunk Confluences

A total of 38 different types of venous confluences forming the venous trunk of Henle were found (Table 2).

Table 2. Chi-Square Analysis of the Distribution of the Henle Trunk Configurations

Confluences	Frequency	Percentage	P-value
RGEV + ASPDV + SRCV	550	24.22	<0.001
RGEV + ASPDV + RCV	512	22.54	<0.001
RGEV + ASPDV	384	16.91	<0.001
RGEV + ASPDV + SRCV + RCV	239	10.52	<0.001
RGEV + SRCV	122	5.37	<0.001
RGEV + ASPDV + RCV + MCV	91	4.0	<0.001
RGEV + ASPDV + SRCV + MCV	54	2.38	<0.001
RGEV + ASPDV + MCV	38	1.67	<0.001
RGEV + ASPDV+ aMCV	34	1.50	<0.001
RGEV + ASPDV + SRCV + RCV + MCV	31	1.37	<0.001
RGEV + ASPDV + SRCV + aSRCV	29	1.28	<0.001
RGEV + ASPDV + RCV + aMCV	26	1.14	<0.001
RGEV + SRCV + RCV	22	0.97	<0.001
RGEV + RCV	22	0.97	<0.001
RGEV + MCV	18	0.79	<0.001
RGEV + SRCV + MCV	14	0.62	<0.001
RGEV + ASPDV + RCV + MCV +aMCV	14	0.62	<0.001
RGEV + ASPDV + RCV + SRCV + aMCV	11	0.48	<0.001
RGEV + SRCV + RCV + MCV	9	0.40	<0.001
RGEV + RCV + MCV	7	0.31	<0.001
RGEV + ASPDV + RCV + ICV	5	0.22	<0.001
RGEV + ASPDV + AIPDV	5	0.22	<0.001
RGEV + ASPDV + SRCV + antral branch	5	0.22	<0.001
ASPDV + SRCV	5	0.22	<0.001
RGEV + ASPDV + ICV	3	0.13	<0.001
RGEV + ASPDV + SRCV + ICV	3	0.13	<0.001
RGEV + ASPDV + SRCV + AIPDV	3	0.13	<0.001
RGEV + ASPDV + sRCV + aMCV	2	0.09	<0.001
RGEV + ASPDV + RCV + MCV + ICV	2	0.09	<0.001
RGEV + ASPDV + RCV + MCV	2	0.09	<0.001
RGEV + ASPDV + SRCV + RCV + ICV	2	0.09	<0.001
RGEV + AIPDV	1	0.04	<0.001
RGEV + ASPDV + SRCV + MCV + ICV	1	0.04	<0.001
RGEV + ASPDV + RCV + SRCV + aSRCV	1	0.04	<0.001
RGEV + ASPDV + SRCV+ retropyloric v.	1	0.04	<0.001
RGEV + ASPDV + SRCV + MRCV	1	0.04	<0.001
RGEV + double RCV	1	0.04	<0.001
RGEV + RCV + ICV	1	0.04	<0.001

The GPC type of the trunk, which, as mentioned above, is the most common, comprises a variety of 25 venous combinations, with RGEV+ASPDV+SRCV or RCV being the most frequent (33.13% and 30.84%, respectively) (Figure 2).

Although the GP type comprises 3 different vein confluences, the RGEV + ASPDV combination accounts for 98% of cases (Table 1). The GC type consists of 9 different vein confluences, in which the RGEV + SRCV combination demonstrates the highest frequency (56.48%), followed by the RGEV + RCV (10.19%) (Figure 3).

The ASPDV + SRCV tributary confluence is the only one reported for the PC combination

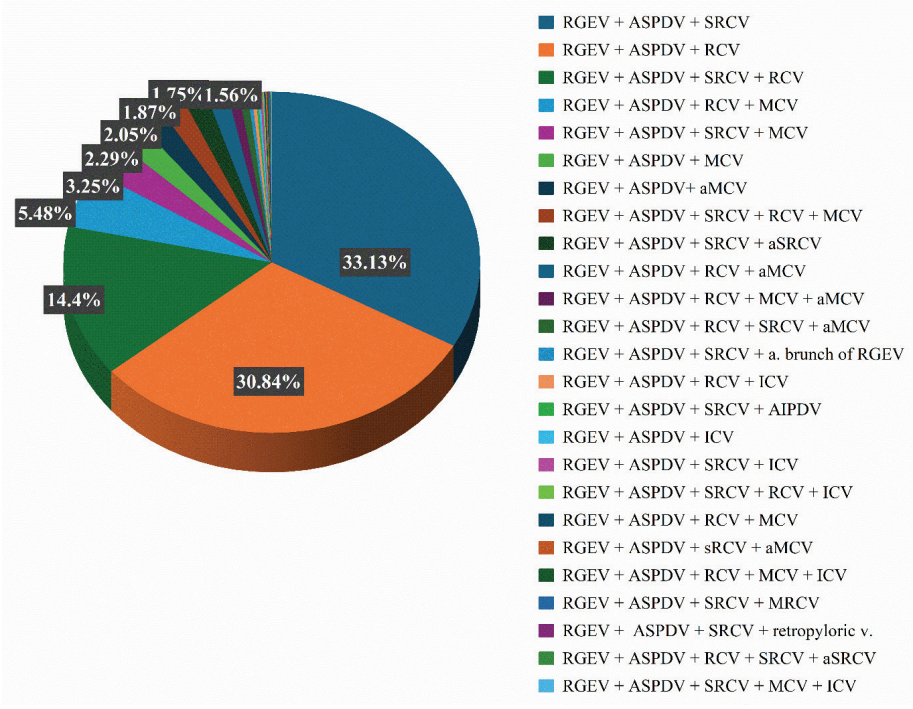

Figure 2. Distribution of the Henle trunk configurations forming the gastropancreatocolic (GPC) type.

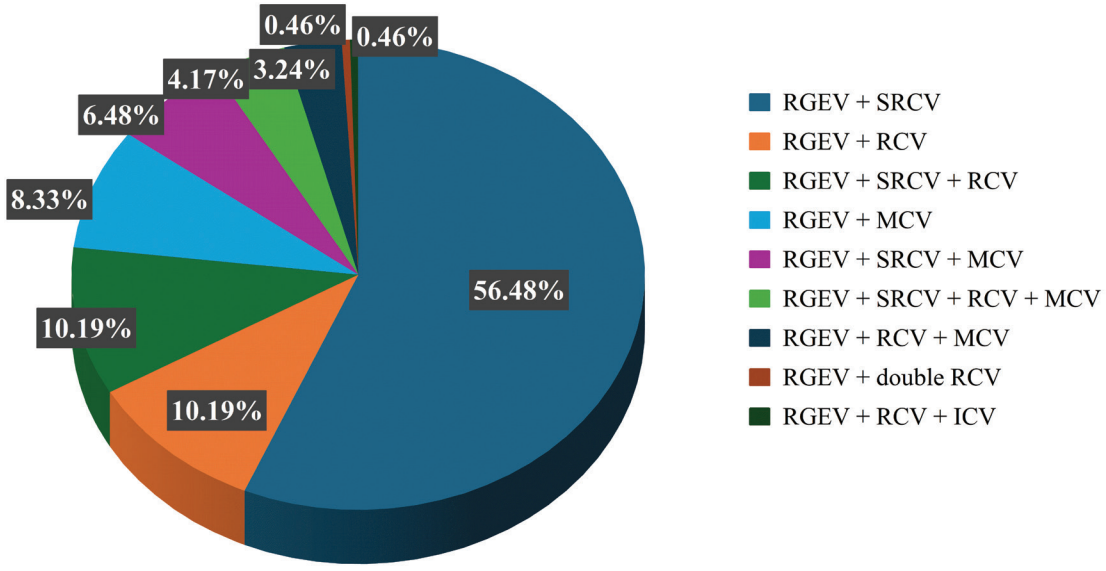

Figure 3. Distribution of the Henle trunk configurations forming the gastrocolic (GC) type.

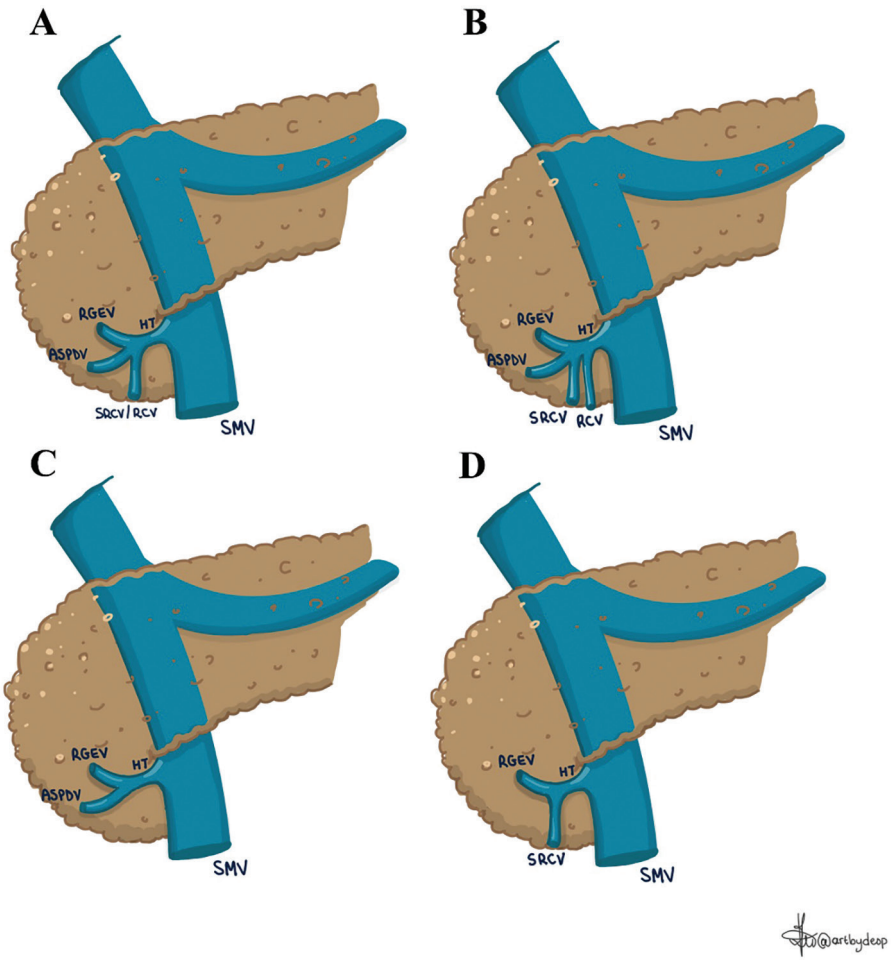

Figure 4. Tributaries of the Henle trunk. (A) Gastropancreatocolic type with a single colic vein; (B) Gastropancreatocolic type with two colic veins; (C) Gastropancreatic type; (D) Gastrocolic type. HT=Henle trunk; RGEV=Right gastroepiploic vein; SRCV=Superior right colic vein; RCV=Right colic vein; ASPDV=Anterior superior pancreaticoduodenal vein; SMV=Superior mesenteric vein.

(Table 1). Overall, the most frequent vein confluence is RGEV+ASPDV+SRCV, accounting for 24.21% of the combinations, followed by RGEV+ASPDV+RCV at 22.54%. Although the GPC type is the most common, with its two main combinations (RGEV+ASPDV+SRCV or RCV) reaching 46.75% of all tributary confluences, the GP variation RGEV+ASPDV is the third most frequent confluence of the Henle trunk, with 16.90% of all vein combinations. The distributions of all the variation percentages are shown in Table 2. A chi-square test was performed, which revealed a high value ($P<0.001$), confirming that certain confluences occur far more frequently than others (Table 2). Figure 4 presents schematic drawings of the four most common Henle trunk configurations based on their venous tributary composition.

Discussion

The Henle trunk is an intricate three-dimensional anatomical structure resulting from the merging of the gastric, colic, and pancreatic veins, converging into the superior mesenteric vein (SMV) at an average distance of 2.2 cm from the inferior margin of the pancreas (19). Due to its considerable variability and often challenging accessibility, insufficient anatomical understanding can lead to inadvertent injury and substantial hemorrhage during abdominal surgeries (20, 31). However, a

well-defined trunk can serve as a vital reference point for surgeons, particularly in minimally invasive laparoscopic procedures (18). In recent years, numerous intraoperative (13, 24) and imaging investigations (14, 15, 29) have been conducted, involving extensive case studies that have enhanced the detailed characterization of the Henle trunk.

The morphological characteristics of the Henle trunk have long been debated due to the notable variability in its tributaries and the diverse anatomical definitions proposed by various research teams. In this study, the Henle trunk is defined as the confluence of the gastric, colic, and pancreatic veins draining into the SMV, comprising four primary types: the gastropancreatocolic (GPC), gastropancreatic (GP), gastrocolic (GC), and pancreatocolic (PC) trunk. This terminology contrasts with the original description by Henle (2), which equated the gastrocolic trunk with the Henle trunk rather than classifying it as a subset, further clarifying that the pancreatic vein may not always be present in the trunk, as noted by other scholars (11, 13).

The investigation involved 2,454 individuals, of whom 1,452 were sourced from studies conducted in the last six years. A 92.54% prevalence of the trunk was observed, aligning with numerous prior studies (4, 11, 22, 24, 26), although it is slightly elevated owing to more recent findings. The results stem from three analytical approaches—cadaveric, intraoperative and imaging—showing similar percentages of trunk presence (90.5%, 95%, and 91.2%, respectively).

Over two-thirds of Henle cases (73.09%) fall under the gastropancreatocolic (GPC) type, consistent with earlier research (5, 6, 10, 25) and more recent studies (13, 14, 28, 29). This figure is higher than that reported in previous review articles (32-34), reflecting an increased frequency of the GPC type in contemporary literature. The GPC type has consistently been identified as the most prevalent, with the sole exception being the analysis by Alsabilah et al. (23), in which the GPC trunk comprised only 34.5% of the patient population. The GP and GC types were found to be significantly less common than the GPC type, accounting for 17.17% and 9.51% of the cases, respectively. These findings align with those of earlier reviews and recent analyses (32, 13).

In this study, the most frequent confluences of the gastropancreatocolic type included those featuring RGEV, ASPDV, and RCV or SRCV. The combinations involving SRCV and/or RCV colic veins constituted 57.27% of all venous arrangements. Cadaveric, operative, and imaging studies yielded comparable findings (52.9%, 55.47%, and 61.02%, respectively). The combination of RGEV+ASPDV+SRCV emerged as the most common type in 9 of the 21 publications reviewed (4, 10, 11, 14, 18, 21, 22, 27, 30), while RCV appeared in 6 of those studies (6, 13, 24, 26, 28, 29). The pooled prevalence of SRCV was slightly higher (33.13%) than that of RCV (30.84%) within the GPC Henle trunk. Surgeons should be aware that while GPC is the predominant Henle type, the GP variation containing RGEV and ASPDV ranks as the third most frequent, making up 16.9% of all Henle confluences.

Conclusions

The Henle gastrocolic trunk is an anatomical structure with a high prevalence that can be used as a landmark during pancreatic or colorectal resections and other abdominal procedures. Our findings confirmed the significant heterogeneity of venous configurations. Precise knowledge of venous anatomy in the GTH region is essential for improving surgical safety and minimizing intraoperative bleeding.

What Is Already Known on This Topic:

The gastrocolic trunk of Henle (GTH) is a venous confluence located at the inferior pancreatic border that drains into the superior mesenteric vein. The complex vascular anatomy of the structure is of major clinical importance during minimally invasive colorectal and pancreatic surgery, in which inadvertent injury can lead to significant hemorrhage. Cadaveric, intraoperative, and imaging studies have identified numerous variations in GTH anatomy. However, the reported prevalence and configuration patterns vary considerably in the literature, partly due to differences in definitions and classification systems.

What This Study Adds:

This systematic review includes 21 studies and the largest number of reported cases to date (2454 cases), providing the most comprehensive analysis of Henle trunk morphology. By integrating 1452 new cases re-

ported in the last six years, in operative and imaging studies, it contributes to precise knowledge of the trunk anatomy. Moreover, it offers a unified classification system (GPC, GP, GC, and PC) and documents 38 venous confluences, quantifying their prevalence. This approach resolves previous inconsistencies in definitions, updates the literature, and provides a clear anatomical framework for improving surgical planning and safety.

Authors' Contributions: Conception and design: GS and DC; Acquisition, analysis and interpretation of data: GS and DC; Drafting the article: GS, DF and DC; Revising it critically for important intellectual content: DF, GT and TT; Approved final version of the manuscript: GS, DC, DF, GT and TT.

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Mini-Review
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Appendiceal Neuroendocrine Tumors in Children and Adolescents

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Abstract

Objective. To synthesize current evidence on the diagnosis, histopathological evaluation, clinical features, management, and follow-up of appendiceal neuroendocrine tumors (aNETs) in children and adolescents, and to outline key differences from their adult counterparts. **Background.** Pediatric aNETs are rare gastrointestinal neoplasms that typically exhibit an indolent clinical course with minimal risk of recurrence or metastasis. Their biological and prognostic features differ from those in adults, limiting the applicability of adult-derived guidelines in children. **Methods.** A mini review of the current literature was conducted, focusing on epidemiology, clinical presentation, diagnostic workup, key pathological features, surgical management, and follow-up strategies for pediatric aNETs. **Discussion.** Contemporary evidence supports a de-escalated, risk-adapted approach to management, with simple appendectomy being curative in most cases. Multidisciplinary Team (MDT) discussion remains critical for atypical or borderline cases requiring individualized decision-making. Differences from adult aNETs highlight the need for pediatric-specific clinical decision-making. **Conclusion.** Early recognition, accurate histopathologic evaluation, and tailored surgical management are essential to optimize outcomes for children and adolescents with aNETs.

Key Words: Appendix ▪ Neuroendocrine ▪ Neoplasms ▪ Children and Adolescents.

Introduction

Appendiceal neuroendocrine tumors (aNETs) are very rare neoplasms in children and adolescents, yet they represent the most frequent gastrointestinal epithelial tumors in this age group (1). Historically referred to as "carcinoids," aNETs are now recognized as a heterogeneous group of well-differentiated neuroendocrine neoplasms with distinct clinical, pathological, and molecular features (1, 2). Despite growing awareness, pediatric-specific data remain limited, and adult-derived guidelines might not adequately capture the unique biological and clinical aspects of pediatric aNETs (3-5).

Epidemiology

The incidence of pediatric aNETs is reported to range between 1:100,000 and 1.14:1,000,000 children per year (1). The precise frequency among all appendectomies remains uncertain. In adults, it is estimated at around 0.2%, whereas in children, the reported rate is 0.169% (1, 6). More recently, a multicenter study in eight U.S. tertiary hospitals reported a slightly higher incidence of 0.4% of all appendectomy specimens (4). The median age at diagnosis is 12 to 14 years, with a slight female predominance (4, 5).

Clinical Presentation

Pediatric aNETs typically present incidentally during appendectomy for suspected acute appendicitis or abdominal pain (4, 6). Symptoms are usually nonspecific, including right lower quadrant pain, nausea, vomiting, and occasional fever (6, 7). Larger tumors (>2 cm) may manifest with

palpable abdominal mass, sometimes mimicking other gastrointestinal malignancies (8, 9). Unlike adults, pediatric aNETs are almost always localized to the appendix at diagnosis, and carcinoid syndrome is exceptionally rare in this age group (4, 5). Multifocality is rare in children, in contrast to adult series (4, 10).

Pathology and Molecular Features

Complete processing of the appendix is mandatory. Pediatric aNETs are typically well-differentiated, low- to intermediate-grade tumors with neuroendocrine morphology, characterized by uniform cells with round nuclei, granular chromatin, and eosinophilic cytoplasm. Immunohistochemistry confirms neuroendocrine differentiation with chromogranin A, synaptophysin, and often CD56 positivity (Figure 1-6) (11, 12).

Additional markers, such as serotonin, glycentin, peptide YY, and somatostatin receptor subtypes, may be employed to characterize tumor subtypes (1). Mitosis and Ki-67 index are usually low (<3%), consistent with the grade 1 World Health Organization (WHO) Classification of Tumours; grade 2 tumors are rare in children (Table 1) (2).

Most pediatric aNETs are localized at the tip of the appendix, with base involvement being uncommon (3, 4). Tumor size is an important prognostic factor, with lesions ≥2 cm associated with higher risk of lymphovascular invasion or nodal involvement (10, 13).

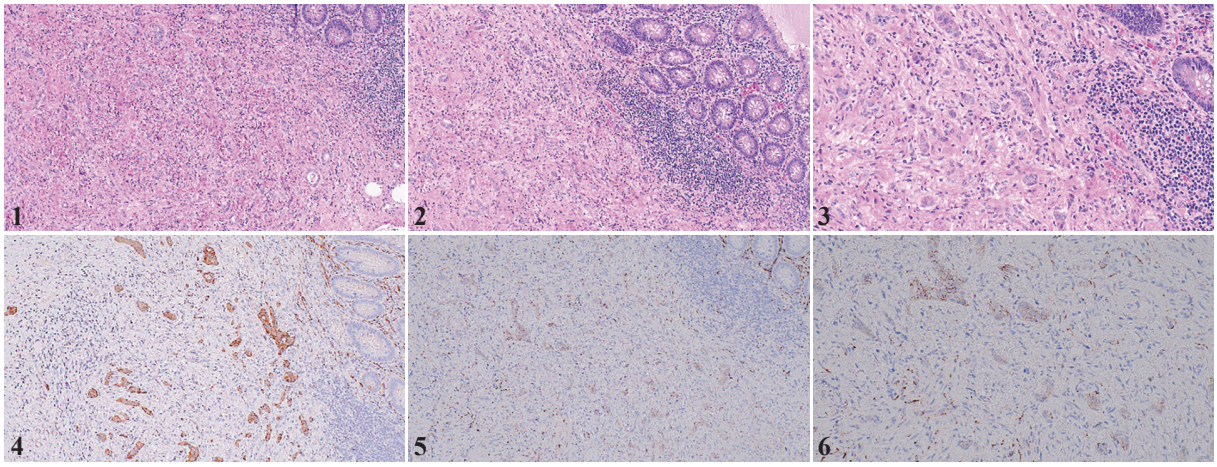

Figure 1-6. Appendiceal neuroendocrine tumors – Histopathological and immunohistochemical features.

Figure 1–3 (1, 2: 10×, 3: 20×). Hematoxylin and eosin (H&E)–stained sections show a well-differentiated neuroendocrine tumor (NET) of the appendix involving the lamina propria. The tumor is composed of a uniform population of round cells with finely stippled chromatin, arranged in predominantly tubular structures with focal trabecular and ribbon-like growth patterns within a fibrotic stroma. No mitotic figures or areas of necrosis are identified. Immunohistochemical staining for neuroendocrine markers, including synaptophysin (Figure 4: 20×) and CD56 (Figure 5: 20×, Figure 6: 40×), shows diffuse positivity in all tumor cells. (Authors' archive).

Table 1. WHO* Classification of Appendiceal Neuroendocrine Tumors

Terminology	Differentiation	Grade	Mitoses	Ki67† (%)
NET‡ G1	Well Differentiated	Low	<2/2 mm²	<3
NET‡ G2		Intermediate	2-20/2 mm²	3-20
NET‡ G3		High	>20/2 mm²	>20
NEC§ Small Cell	Poorly Differentiated	High	>20/2 mm²	>20
NEC§ Large Cell				

*World Health Organization; †Proliferation index; ‡Neuroendocrine tumor; §Neuroendocrine carcinoma.

Data on molecular profiles in pediatric aNETs molecular profiles are scarce. Adult studies have identified occasional alterations in *TP53* or *SMAD4* affecting cell cycle and TGF-β signaling, while no consistent pediatric-specific mutations have been identified (14).

Diagnosis and Staging

Routine laboratory evaluation is typically unremarkable. Urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), and serum levels of chromogranin A and neuron specific enolase (NSE) may be elevated in bulky residual disease or metastatic spread; however, such presentations have not been described in the pediatric population (10, 15).

Imaging is typically omitted preoperatively, since pediatric aNETs are most often detected incidentally. Ultrasound and computed tomography (CT) can detect appendiceal masses in selected cases (1, 4). Post-appendectomy imaging has a limited value, as ultrasound, CT, and magnetic resonance imaging (MRI) rarely detect residual disease <1 cm or nodal micrometastases (0.2–2 mm). Functional studies, including positron emission tomography (PET)/MRI-CT and somatostatin receptor imaging (SRI; (68Ga)Ga-DOTA-TOC/TATE) may similarly miss microscopic nodal involvement, and routine use of either modality is not recommended in pediatric aNETs (15-17).

aNETs are staged as per the European Neuroendocrine Tumour Society (ENETS)/ the American Joint Committee on Cancer (AJCC) Cancer Staging System Version 9 (10, 18). Staging in children is based primarily on tumor size and local invasion. Nodal (N) and distant metastases (M) staging is generally not applicable, as metastases have not been reported in this population (Table 2).

Management

Most pediatric patients are effectively cured with appendectomy alone, rendering additional surgery unnecessary for preventing local or distant recurrence or improving event-free or overall survival (1). In children, potential risk factors warranting consideration include microscopic residual disease (R1 resection, particularly at the appendiceal base), tumor size >2 cm, grade >2, nodal positivity at appendectomy, and suspicious findings on postoperative imaging, when performed. Other factors commonly applied in adult guidelines – such as lymphovascular invasion, serosal involvement, perforation or tumor rupture, and mesoappendiceal invasion – appear to have limited significance in the pediatric setting (3, 9, 19, 20). Current evidence suggests that appendectomy alone is generally sufficient in these cases, and second surgeries – such as right hemicolectomy, ileocecal resection, or partial cecectomy – are typically unnecessary (1, 21). Only one local relapse has been documented in pediatric series, and complete remission was achieved following surgical resection (22). Multidisciplinary Team (MDT) discussion is strongly recommended in all borderline or complex cases to ensure appropriate, individualized management.

Table 2. Staging of Pediatric Appendiceal Neuroendocrine Tumors

pT*	ENETS†	AJCC‡ Version 9
pT1	T ≤ 1 cm and submucosa or muscularis propria invasion	T ≤ 2 cm in greatest dimension
pT2	T ≤ 2 cm and submucosa or muscularis propria or mesoappendix/subserosa invasion ≤3 mm	T > 2 and ≤ 4 cm in greatest dimension
pT3	T > 2 cm and/or esoappendix/subserosa invasion >3 mm	T > 4 cm in greatest dimension, or with subserosal invasion, or involvement of the mesoappendix
pT4	Perforates serosa/peritoneum, or invades other neighbouring organs	T perforates the peritoneum, or directly invades other adjacent organs or structures

*Pathological tumor stage †European Neuroendocrine Tumour Society; ‡American Joint Committee on Cancer.

Adjuvant therapy is not indicated in children. Prognosis is excellent, with 5- and 10-year overall survival rates approaching 100% (4, 5, 9). Given the rarity of pediatric aNETs, enrollment in international rare tumor registries is recommended to strengthen future evidence.

Follow-Up

Follow-up strategies for pediatric aNETs vary across reported series, and measurement of biochemical markers has not shown benefit in most patients. Similarly, CT/MRI and SRI have limited sensitivity in detecting small-volume or nodal disease and may yield false-positive results, making them unsuitable for routine use. Therefore, surveillance should be tailored to risk. For completely resected tumors <2 cm without additional risk factors, no follow-up is required. For tumors ≥2 cm or those with risk features (R1 resection, grade 2/3, or nodal involvement), annual physical examination with abdominal ultrasound for 5 years is recommended, reserving additional imaging for equivocal or symptomatic cases (1, 15, 17).

Conclusions

Pediatric aNETs are rare, typically indolent neoplasms with excellent prognosis. Most cases are diagnosed incidentally during appendectomy, and complete surgical excision is generally curative. MDT discussion remains essential for optimizing management in borderline or complex cases. Follow-up should be tailored to individual risk. Due to the rarity of these tumors, enrollment in international registries is important to strengthen evidence and guide pediatric-specific management.

What Is Already Known on This Topic

aNETs are rare in children and adolescents but represent the most common gastrointestinal epithelial neoplasms in this age group. They are usually diagnosed incidentally during appendectomy for suspected appendicitis, and almost always present as localized, well-differentiated tumors with an indolent clinical course. Metastatic spread is exceedingly rare and prognosis is excellent. Most pediatric patients are cured with appendectomy alone, whereas several histopathologic factors used in adult guidelines—such as lymphovascular invasion or mesoappendiceal involvement—appear to have limited relevance in children. Despite this, pediatric-specific evidence remains scarce, and current practice is often guided by adult data, which may not fully reflect the unique biological and clinical characteristics of pediatric aNETs.

What This Study Adds

This mini-review synthesizes current evidence on pediatric aNETs and provides a structured, risk-adapted framework for diagnosis, pathological assessment, management, and follow-up. It clarifies which histologic features are prognostically relevant, and emphasizes that most do not require escalation of surgery. The review also highlights the limited value of postoperative imaging and laboratory surveillance, recommending simplified, risk-based follow-up. MDT decision is underscored for borderline cases, and key differences from adult counterparts are outlined to support pediatric-specific clinical decision-making.

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A Case Series and Literature Review
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Surgical Re-Resection for Isolated Local Recurrence of Pancreatic Cancer: A Case Series of 3 Patients and Literature Review

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Abstract

Objective. This retrospective case series study aims to assess the clinical role of surgical re-resection for isolated local recurrence of pancreatic cancer, integrating detailed case presentations with current evidence to clarify patient selection criteria, operative feasibility, and oncologic outcomes. **Case Presentations.** We present three patients with locally recurrent pancreatic cancer who underwent repeat pancreatic resection. Patient 1, who previously underwent distal pancreatectomy for an Intraductal Papillary Mucinous Neoplasm (IPMN)-associated adenocarcinoma, developed a new pancreatic head lesion three years later and underwent pylorus-preserving pancreaticoduodenectomy; histopathology confirmed a small invasive IPMN, and the patient remains alive 8 years after the initial diagnosis and 5 years after the reoperation. Patient 2, who had previously undergone Pylorus-Preserving Pancreaticoduodenectomy for distal bile duct adenocarcinoma, developed recurrent disease in the pancreatic body and tail three years later. He underwent distal pancreatectomy but developed liver recurrence due to hematogenous metastasis one month postoperatively and succumbed 6 months later from generalized widespread disease. Patient 3, who previously underwent a Whipple procedure for IPMN-associated adenocarcinoma, developed a recurrent mass at the pancreatojejunostomy five years later and underwent distal pancreatectomy, with an uneventful recovery. **Conclusion.** Our findings suggest that repeat pancreatic resection may be feasible in carefully selected patients with isolated local recurrence, potentially offering a survival benefit. Strict selection criteria, including the absence of distant metastases, good performance status, and technically resectable disease, appear essential to optimize outcomes, supporting the consideration of surgical re-resection as an option within a multidisciplinary management framework.

Key Words: Pancreatectomy ▪ Pancreatic Neoplasms ▪ Repeat Surgery.

Introduction

Pancreatic cancer is one of the most aggressive malignancies and ranks as the fourth leading cause of cancer-related mortality in both men and women (1, 2). Disease recurrence is common even after initially successful resection, and optimal management of locally recurrent pancreatic cancer remains undefined (3-5). Amidst this lack of consensus, surgical re-resection has historically been underutilized due to technical complexity and limited patient eligibility; however, recent improvements in systematic management have enhanced oncologic control and broadened the applicability of repeat surgery for selected patients (6, 7).

The objective of this study is to present three patients undergoing repeat pancreatic resection, highlighting patient selection, operative feasibility, and oncologic outcomes. The lack of standardized guidelines, as well as a limited amount of published data regarding surgical re-resection for recurrent pancreatic cancer, makes this study clinically relevant.

Methods

The presented cases were obtained through a thorough retrospective review of the existing medical records. Among a cohort of 350 patients who had initially undergone resection for pancreatic adenocarcinoma, three cases were eligible for reoperation after recurrence. Patients were included in this series after being assessed based on predefined inclusion criteria. Precisely, the evaluation of candidates was focused on patients presenting with the absence of distant metastases, adequate performance status, and technically resectable disease. All of the included cases were discussed in a multidisciplinary tumor board, which reached a consensus for the management approach of each patient. Follow-up methods were conducted based on institutional protocol, which consisted of CT imaging and tumor markers every 6 months for two years, and then annually.

Case Presentations

Patient 1

A 59-year-old male patient was found to have a cystic lesion involving the pancreatic body and tail, for which he underwent distal pancreatectomy with splenectomy. Intraoperative exploration revealed no peritoneal or hepatic metastases. The pancreas was transected at the neck, and the spleen was removed en bloc with the distal pancreas. Histopathological examination of the specimen demonstrated a mucinous adenocarcinoma arising in the background of an intraductal papillary mucinous neoplasm (IPMN) of intestinal type with moderate to severe dysplasia. The invasive component measured 4 × 2.5 × 4 cm, confined to the pancreas (pT2N0, AJCC). Resection margins were free of carcinoma, and sixteen regional lymph nodes were negative for metastatic involvement. Six months of adjuvant treatment based on the FOLFIRINOX regimen was established and well tolerated by the patient.

During postoperative yearly follow-up and after 3 years from the initial operation, imaging revealed a new cystic lesion in the pancreatic head, suggestive of a metachronous or multifocal IPMN. The patient subsequently underwent a pylorus-preserving pancreaticoduodenectomy (PPPD) with cholecystectomy. Figure 1 depicts the Computed Tomography (CT) Imaging that the patient underwent in order to show the new lesion (Figure 1).

The resected specimen showed an IPMN of pancreatobiliary type in the pancreatic head, exhibiting low-grade and focal high-grade dysplasia, with a focal area of invasive, moderately differentiated adenocarcinoma measuring <1 cm in greatest dimension. All surgical margins and twelve examined lymph nodes were free of carcinoma (pT1bN0, AJCC). The patient recovered

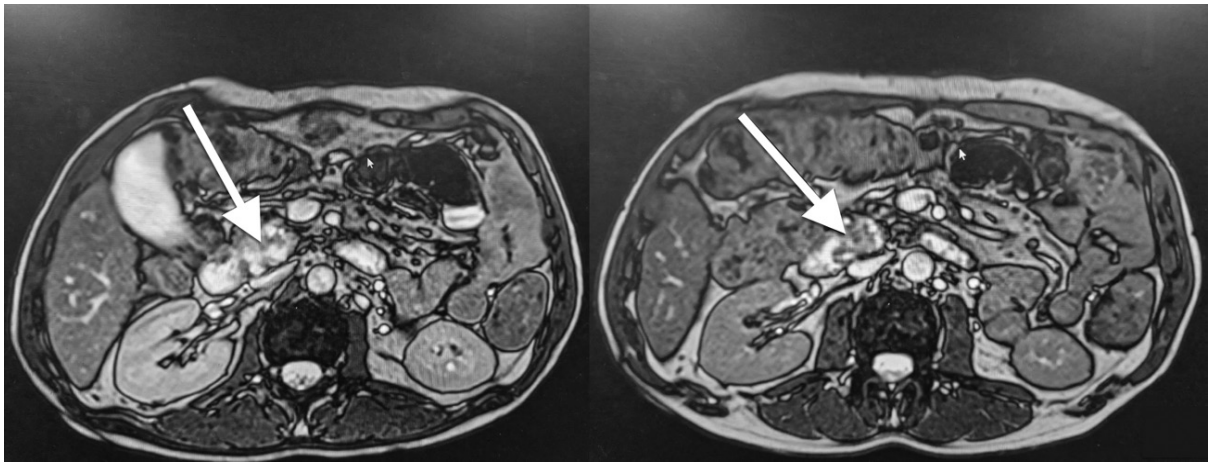

Figure 1. CT of the first patient depicting the new lesion. White arrow showcasing the presence of the lesion on the pancreatic head.

uneventfully following the second operation and is alive and disease-free today, after more than 5 years (~70 months) from the reoperation and 106 months from the initial index surgery.

Patient 2

A 44-year-old man with a history of gallstone pancreatitis and prior cholecystectomy was found to have an obstructive lesion of the distal common bile duct on magnetic resonance cholangiopancreatography (MRCP). Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement and sphincterotomy was subsequently performed. The patient was discussed in a multidisciplinary tumor board and subsequently underwent PPPD.

Intraoperative findings confirmed a resectable lesion of the distal bile duct. Histopathological evaluation revealed a moderately differentiated adenocarcinoma of the distal bile duct with invasion into the pancreatic parenchyma and focal extension into the peripancreatic fat. Perineural and vascular invasion were present, and one of eighteen lymph nodes demonstrated metastatic involvement. Even though resection margins were negative for carcinoma, a High Grade PanIN was detected at the pancreatic neck margin. The disease was staged as pT3N1 (AJCC). The postoperative course was uneventful, and the patient completed twelve cycles of adjuvant chemotherapy (FOLFIRINOX).

The patient was followed according to institutional protocol, consisting of CT imaging and tumor markers every 6 months for two years, and then annually. Three years postoperatively, the onset of recurrent abdominal pain prompted further investigation. A PET/CT scan revealed a hypermetabolic lesion in the pancreatic tail measuring 2.7 × 3.3 cm. Endoscopic ultrasound (EUS) confirmed a focal mass in the pancreatic body with extrapancreatic extension, and fine-needle biopsy suggested recurrent adenocarcinoma. Figure 2 contains the PET/CT scan (Figure 2).

The patient subsequently underwent distal pancreatectomy with splenectomy after discussion and consensus by a multidisciplinary team. Intraoperatively, dense adhesions from the previous Whipple procedure and extensive collateral venous circulation secondary to left-sided portal

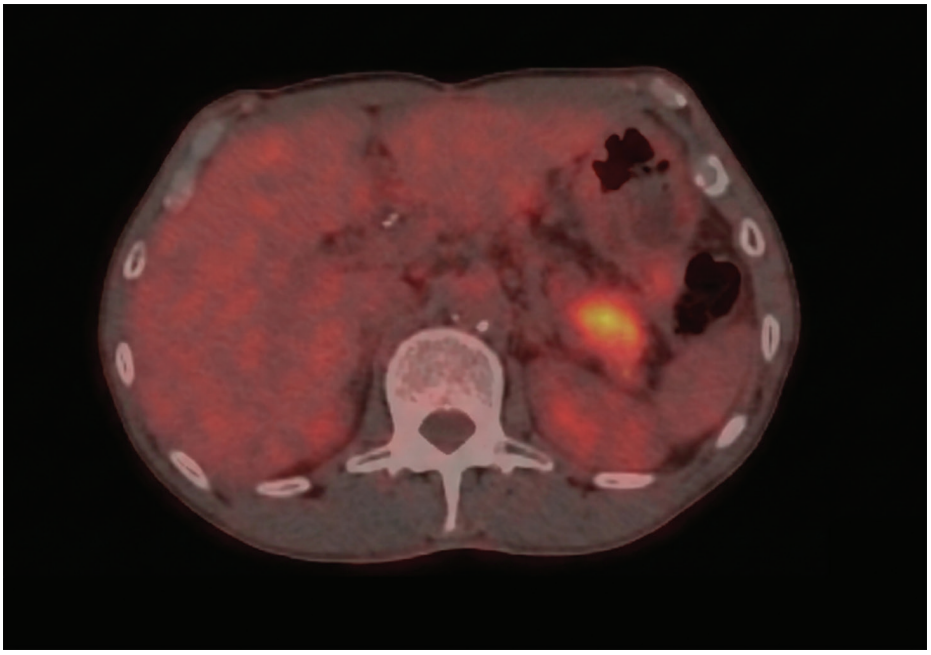

Figure 2. PET/CT scan showcasing the hypermetabolic lesion on the pancreatic body/tail.

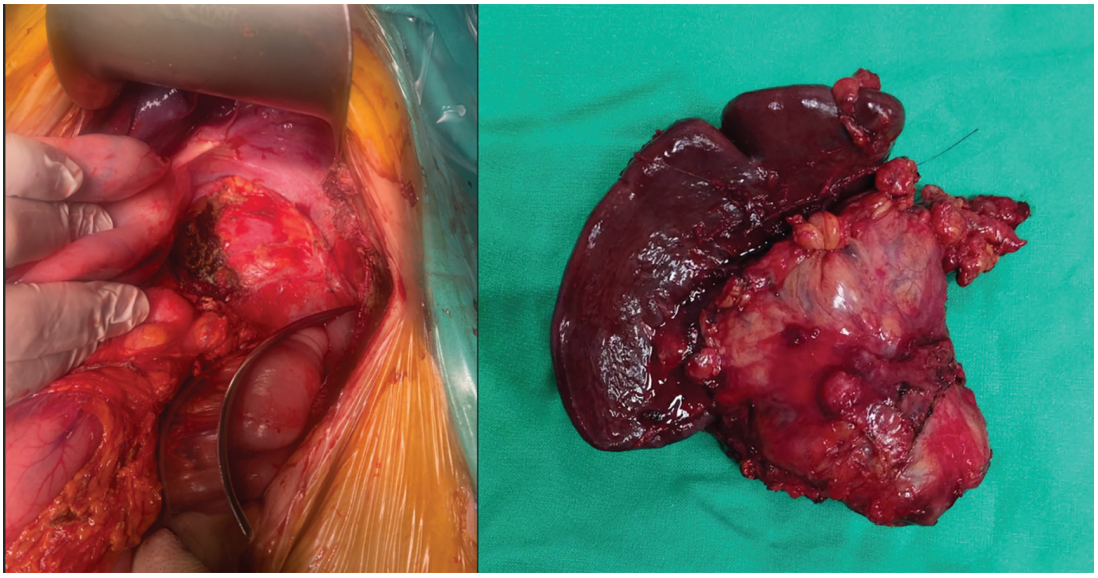

Figure 3. Left: intraoperative image of the distal pancreatectomy of the second patient. Right: specimen removed following the completion of the surgery.

hypertension were encountered, rendering the procedure technically demanding. Figure 3 contains an intraoperative picture (Figure 3).

Histopathology demonstrated a poorly differentiated adenocarcinoma of the pancreatic body and tail, measuring 5 cm in greatest dimension, with vascular invasion and focal extension to the splenic hilum. The anterior surface was microscopically disrupted by tumor infiltration, and two of twenty examined lymph nodes were positive for metastasis (pT2N1). The resection margin contained high-grade pancreatic intraepithelial neoplasia (PanIN). One month later, the patient developed metastatic spread to the liver, and although chemotherapy was offered as a palliative treatment strategy, the patient passed away 6 months later due to widespread disease.

Patient 3

A 63-year-old man with a history of pancreatic head adenocarcinoma treated with pancreaticoduodenectomy (Whipple procedure) 4 years earlier was referred for surgical management of a newly detected lesion in the pancreatic remnant. The patient had initially undergone a standard Whipple procedure for a moderately differentiated ductal adenocarcinoma of the pancreatic head, arising in association with a mixed-type IPMN exhibiting high-grade epithelial dysplasia. Histopathologic examination revealed tumor extension into the peripancreatic adipose tissue and focal perineural invasion. The pancreatic neck margin contained foci of high-grade IPMN (PanIN-3), whereas the gastric, duodenal, and common bile duct margins, as well as all examined lymph nodes (14 nodes), were free of carcinoma. The tumor was staged as pT2N1 (AJCC). The postoperative course was uneventful, and the patient subsequently received adjuvant chemotherapy based on FOLFIRINOX.

Five years after the index operation, during routine annual surveillance (performed per institutional protocol using CT imaging and tumor markers) and while the patient was asymptomatic, imaging revealed a new mass at the site of the previous pancreatojejunostomy. Operative exploration revealed dense adhesions from the prior surgery. The pancreatojejunostomy and adjacent pancreatic body were carefully dissected, and a distal pancreatectomy with splenectomy was performed, including resection of the splenic hilum.

Histopathologic analysis confirmed a recurrent ductal adenocarcinoma measuring 3.5 cm, located intraparenchymally at the pancreatojejunostomy,

Table 1. Diagnosis, Surgical Management, and Outcomes of the Included Patients

Parameters	Patient 1	Patient 2	Patient 3
Age	59	44	63
Gender	Male	Male	Male
Initial Diagnosis	IPMN*-associated adenocarcinoma on the pancreatic body and tail	Distal bile duct adenocarcinoma	IPMN* pancreatic head adenocarcinoma
Initial Surgery	Distal Pancreatectomy with splenectomy	PPPD†	Pancreaticoduodenectomy
Diagnosis of Recurrence	IPMN* Adenocarcinoma on the pancreatic head	Adenocarcinoma on the pancreatic body and tail	Ductal Adenocarcinoma
Surgery for Recurrence	PPPD†	Distal Pancreatectomy with splenectomy	Distal Pancreatectomy with splenectomy
Outcome	Alive and disease-free, 70 months postoperatively	Deceased 6 months later	Alive and disease-free, 10 months postoperatively

*Intraductal Papillary Mucinous Neoplasm; †Pylorus-Preserving Pancreaticoduodenectomy.

without invasion of the jejunal wall. The carcinoma infiltrated and disrupted the anterior pancreatic surface but spared the posterior margin. One lymph node out of 6 were positive for metastatic disease (pT2N1, AJCC). The remaining pancreatic parenchyma demonstrated exocrine atrophy and focal endocrine hyperplasia, while the spleen showed capsular rupture with hemorrhagic changes. All resection margins were free of tumor. The patient recovered uneventfully after surgery and is still alive and disease-free to this day, almost 5 years since the initial operation and 10 months following the second operation. The main characteristics of all 3 patients are presented in Table 1.

Results

After the assessment of 350 candidates for reoperation, 3 patients (<1%) underwent completion pancreatectomy after being diagnosed with recurrent pancreatic malignancy. The average age of our case series was 55.3 years, while the mean interval between the initial operation and the re-resection was found to be 41.4 months. Patient 3 presented with the greatest time interval between the two operations (50.5 months), which was almost 1.5 times longer than the other 2 cases. Regarding perioperative outcomes, all 3 patients had an uncomplicated course, with no reported morbidities. Histopathological assessment revealed significant variability in tumor burden, with tumor size ranging from <1 cm to 5 cm. Despite this size variation, R0 resection was achieved in all 3 operations. Furthermore, metastatic lymph node involvement was identified in two of the three patients (66%). In terms of long-term oncologic outcomes, results were heterogeneous: one patient succumbed to disease progression at 6 months, while the remaining two patients are alive and disease-free at 70 and 10 months, respectively.

Discussion

Recurrent pancreatic cancer after initial surgical resection poses a significant therapeutic challenge, as the decision between systemic chemotherapy and surgical reoperation is often complex. In patients with a poor overall prognosis, aggressive interventions may confer more harm than benefit due to the high morbidity (8). However, growing evidence suggests that both chemotherapy and repeat resection can be acceptable management options in selected cases. A systematic review and meta-analysis by Groot et al. reported that while surgical reoperation can be technically demanding, particularly in cases with vascular involvement, it remains an effective and safe therapeutic option when carefully indicated (9). Consistent with the recommendations by Molletta et al., who advised that re-resection should be considered in patients without distant metastases to the liver, lung, bone, or peritoneum, to optimize potential

survival benefit, all three of our patients, who had no evidence of distant metastasis, were carefully selected for reoperation (5). Although multidisciplinary management is often advocated, no standardized international guidelines currently define optimal treatment for this subset of patients (10). Therefore, surgical reoperation should be reserved for patients who fulfill a certain set of criteria, which will be discussed in the next paragraphs.

Our case series illustrates the feasibility of reoperation for locally recurrent pancreatic cancer in three carefully selected patients. Reddy et al., in a large series of over 500 reoperations following pancreatectomy, reported that approximately 1% of all patients underwent late reoperation due to recurrent disease, typically within 1–2 years of the index surgery (11). In contrast, all three of our patients underwent reoperation roughly 3.5 years after their initial procedure, aligning more closely with the pooled analysis by Choi et al., which reported a mean interval of 41.3 months (3.44 years) between the two operations (12).

Several studies have compared outcomes of surgical re-resection versus nonsurgical management. Kleef et al. found that surgical intervention nearly doubled median overall survival (17 vs. 9 months) compared to chemotherapy alone (3). Similarly, Miyazaki et al. demonstrated that the two-year survival was markedly higher in the surgical group (61% vs. 19%), while Serafini et al.'s meta-analysis confirmed a mean overall survival of 29 months and post-recurrence survival of 15 months following reoperation (13, 14).

Comparable results were reported by Yamada et al., who showed a five-year survival increase from 3% in nonsurgical patients to 15% in those who underwent reoperation (15). Kim et al. observed a similar benefit, with median survival of 28 months in surgically treated patients, versus 12 months in those managed non-operatively (16). Strobel et al. further demonstrated that patients with isolated local recurrence achieved a median survival of 26 months compared to 10.8 months with conservative therapy (17). The outcomes of our case series are consistent with the beneficial role of surgical management in survival extension that is reported in the literature, as Patient 1 exceeded the median survival benchmarks of the aforementioned major series. Similarly, it should also be mentioned that Patient 3 remains clinically well and disease-free, 10 months after the operation. Collectively, these studies support the notion that surgery may retain a potentially curative role for highly selected patients with localized recurrence after pancreatectomy (17).

Survival data from recent literature further reinforce the potential benefit of reoperation. Hajibandeh et al., in a systematic review, reported 1-, 2-, 3-, and 5-year survival rates of 70.6%, 38.8%, 20.2%, and 9.2%, respectively (18). Zhou et al. reported slightly higher rates, 82.2%, 49.2%, and 40.6% at 1, 3, and 5 years, respectively, underscoring that selected patients can achieve long-term survival after reoperation for recurrent disease (10).

The divergent postoperative courses of patients 1 and 3, compared to the second patient, highlight the crucial role of prognostic factors in identifying suitable candidates for reoperation. Nienhuser et al. highlighted several favorable indicators: age below 65 years, low BMI (<20 kg/m^2), low preoperative CA19-9 levels, completion of adjuvant therapy, R0 resection, and recurrence within the pancreatic remnant, and a long interval (>10 months) since the index resection (6). Favorable molecular subtypes, such as IPMN-associated carcinoma and KRAS- or SMAD4–wild-type tumors, are also linked to improved outcomes (19, 20). All three of our patients exhibited multiple favorable factors, including age <65, long disease-free interval, R0 resection at reoperation, and localized recurrence. Patients 1 and 3 had IPMN-associated tumors, a subgroup generally associated with more indolent behavior. Conversely, patient 2 demonstrated adverse features that are associated with poorer outcomes, such as poor differentiation, vascular and perineural invasion, and nodal metastasis, portending a less favorable prognosis despite technically successful resection. These adverse characteristics may explain the outcome of patient 2, who succumbed to the disease 6 months later. In retrospect, initiation of neoadjuvant chemotherapy could have been a better alternative

Table 2. Data Regarding Survival Benefit of Surgical Reoperation for Recurrent Pancreatic Cancer

Study	Median Survival for Surgery (months)	Median Survival for non-surgery (months)	1-year survival	2-year survival	3-year survival	5-year survival
Kleef (3)	29.0	14.5	-	67.3	-	5.6
Hajibandeh (10)	-	-	70.6	38.8	20.2	9.2
Serafini (13)	28.7	-	-	-	-	-
Miyazaki (14)	25.0	9.3	-	61	-	41
Yamada (15)	26.0	14.0	-	-	-	15
Kim (16)	26.0	10.8	74.5	31.4	-	21.7
Strobel (17)	26.0	10.8	57.4	27.1	14.1	-
Zhou (21)	-	-	82.2	-	49.2	40.6

to upfront surgery. This example showcases the narrow clinical spectrum in which reoperation can be beneficial. Only a few unfavorable characteristics can significantly impact patient prognosis and survival. Detailed data are presented in Table 2.

Although numerous studies report a clear survival advantage for surgical resection in cases of locally recurrent pancreatic cancer, additional factors such as postoperative quality of life, morbidity, and long-term functional outcomes must also be considered (6). Other fundamental factors that guide this decision include the anatomical resectability of the recurrent lesion, the patient's overall performance status, and existing comorbidities (8). Hence, patient selection criteria must not be unidimensional; rather, they require a multifaceted assessment that balances the technical feasibility with the projected quality of life and oncologic outcome.

As discussed earlier, patients with a low likelihood of achieving an R0 resection should not be considered for repeat surgery and are instead better suited for alternative therapeutic approaches. Both the Zhou Y et al. trial (8) and Okusaka et al. (21) review agree that the alternative options of chemoradiotherapy and stereotactic body radiotherapy could act as a useful tool to provide better results for the patient with minimal invasion. Even though the findings of Groot et al.'s review clearly showcase the survival advantage that surgical resection offers, it also highlights the safety and adequate efficacy of the other two options (2). The patients presented in our case series are a prime example of the necessity to apply strict eligibility criteria in order to establish the best possible management approach, as unnecessarily aggressive procedures could significantly impact the patient's prognosis. Therefore, despite the positive data regarding the postoperative trajectory of reoperated patients, the eligibility of such individuals is very limited.

Conclusion

Our case series contributes to the growing body of evidence by illustrating real-world examples of pancreatic reoperation in carefully chosen patients with isolated local recurrence. These 3 cases, along with their outcomes (positive and negative), indicate that repeat pancreatic resection is feasible and may offer survival benefits in highly selected candidates. However, strict adherence to selection criteria, specifically the absence of distant metastases, preserved performance status, and technical resectability, appears critical to optimizing outcomes. While applicable to a limited patient subset, surgical re-resection warrants consideration as a potentially valuable option within a multidisciplinary management framework. Additional multicenter and prospective studies need to be conducted in order to validate our findings and further refine patient selection criteria.

What Is Already Known on This Topic:

Recurrent pancreatic cancer after initial surgical resection is a frequent and clinically challenging scenario, with patients often facing poor overall prognosis. Standard management typically involves systemic chemotherapy or radiotherapy, which can provide disease control but offer limited long-term survival, particularly in cases of isolated local recurrence. Surgical re-resection has historically been underutilized due to its technical complexity, prior operative adhesions, and the limited subset of patients suitable for intervention. However, accumulating evidence demonstrates that reoperation is feasible and can confer meaningful survival benefits when carefully selected patients are treated. Favorable outcomes are generally associated with localized recurrence without distant metastases, good performance status, adequate disease-free interval from the initial surgery, R0 resection, and indolent tumor biology such as IPMN-associated carcinoma. While survival is variable and dependent on individual prognostic factors, selected patients undergoing repeat pancreatic resection can achieve prolonged survival compared to nonsurgical management. High-level evidence regarding the management of locally recurrent disease is limited. Surgical re-resection is a valid option for resectable recurrence, whereas stereotactic radiotherapy and chemoradiation can be considered for unresectable cases.

What This Study Adds:

This study adds real-world evidence on the feasibility and outcomes of repeat pancreatic resection for isolated local recurrence. By presenting three cases with varied pathological features and postoperative courses, it highlights critical factors influencing patient selection, including the absence of distant metastases, favorable tumor biology, long disease-free interval, and technical resectability. The cases illustrate that, when stringent criteria are applied within a multidisciplinary framework, surgical re-resection can be performed safely and may offer meaningful survival benefit for selected patients. Additionally, the study reinforces the limited but potentially curative role of surgery in recurrent pancreatic cancer.

Authors' Contributions: Conception and design: SD and NT; Acquisition, analysis and interpretation of data: SD, NT, and DC; Drafting the article: SD, NT and AS; Revising it critically for important intellectual content: DC and TT; Approved final version of the manuscript: SD, NT, AS, and TT.

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Case Report
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A Rare Cadaveric Case Report of the Median Nerve Passing Through the Brachialis Muscle

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Abstract

Objective. To describe a rare cadaveric topographical variation of the median nerve (MN) involving an atypical relationship with the brachialis muscle (BM). Such variations, although uncommon, may complicate surgical procedures, regional anesthesia, and imaging interpretation. This report documents a variation in which the MN traverses the BM without providing motor innervation. **Case Report.** During the routine dissection of the right upper limb of a 75-year-old male donated cadaver, a unilateral (right-sided) topographical variation of the MN was identified. The MN diverged from its usual close association with the brachial artery (BA) and followed a medial and posterior course toward the BM. Within the middle third of the arm, the nerve penetrated a macroscopically distinct bundle of BM fibers, traversed the muscle belly, and exited in its distal third. Distally, the MN resumed a superficial course, re-approached the BA, and continued normally through the cubital fossa. No motor or accessory branches from the MN to the BM were identified during its intramuscular course. The surrounding muscle fibers closely encircled the nerve along its intramuscular segment, indicating a restricted anatomical corridor. The musculocutaneous nerve, BA, and the remaining neurovascular structures followed their typical anatomical pathways. **Conclusion.** This anatomical configuration may represent a potential anatomical substrate for proximal MN irritation or compression and may clinically resemble pronator teres syndrome. Awareness of such variants is important for clinicians evaluating MN neuropathies and for surgeons, anesthesiologists, and radiologists working in the anterior compartment of the arm.

Key Words: Median Nerve ▪ Brachialis Muscle ▪ Entrapment Neuropathy ▪ Anatomical Variation.

Introduction

The median nerve (MN) is a terminal branch of the brachial plexus formed by contributions from the lateral and medial cords. In the arm, it typically descends in close association with the brachial artery (BA), initially lying lateral to the artery before crossing anteriorly to reach its medial side. In the distal arm, the MN lies superficial and medial to the brachialis muscle (BM), which does not normally innervate.

Although uncommon, several topographical and morphological variations involving the relationship between the MN and BM have been reported. These include the presence of an accessory MN branch supplying the BM (1), variants in which both the MN and BA traverse the BM (2), and passage of the MN through a musculofascial tunnel formed by the BM and the medial intermuscular septum, frequently associated with muscular innervation (3). Penetration of the BM by the MN following separation from the BA has been described only rarely in the literature (4). Recognition of such variants is clinically important, as deviations from the typical MN course may predispose the nerve to irritation or compression and complicate surgical approaches, regional anesthesia, and radiological interpretation.

In this report, we describe a rare cadaveric case in which the MN traversed the BM without providing motor innervation.

Case Report

During the routine dissection of the right upper limb of a 75-year-old formalin-fixed Greek male cadaver donated to the Department of Anatomy and Surgical Anatomy at the Medical School, Aristotle University of Thessaloniki, an unusual unilateral course of the MN was observed. The cadaver had been donated pre-mortem with written informed consent, and the study complied with institutional ethical standards for anatomical donation. The anomaly was evident at the level where the short and long heads of the biceps brachii (BB) muscle fused. At this point, the MN, comprised of two lateral roots and one medial root, diverged from its typical close association with the BA (Figure 1), coursing medially and posteriorly toward the BM (Figure 2).

At the level of the origin of the BM to the proximal portion of the distal third of the humerus, the MN coursed deeper toward the brachialis fascia. Within the middle third of the BM, a macroscopically distinct bundle of muscle fibers projected anteriorly and was penetrated by the MN. The MN traversed the muscle belly and exited at the distal third of the humerus. Beyond this point, the MN resumed a more superficial course, reapproached the BA, and continued its typical anatomical pathway through the cubital fossa, near the midpoint of the pronator teres muscle. The morphological features of this variation are illustrated in Figure 3.

Further meticulous macroscopic dissection confirmed that no motor or accessory branches arising from the MN supplied the BM during its intramuscular course. The surrounding muscle fibers closely encircled the nerve along its intramuscular segment, indicating a restricted anatomical corridor. Because cadaveric findings cannot replicate in vivo biomechanical conditions, no definitive conclusion regarding functional nerve compression can be drawn; however, this configuration may represent a potential anatomical substrate for MN irritation under physiological

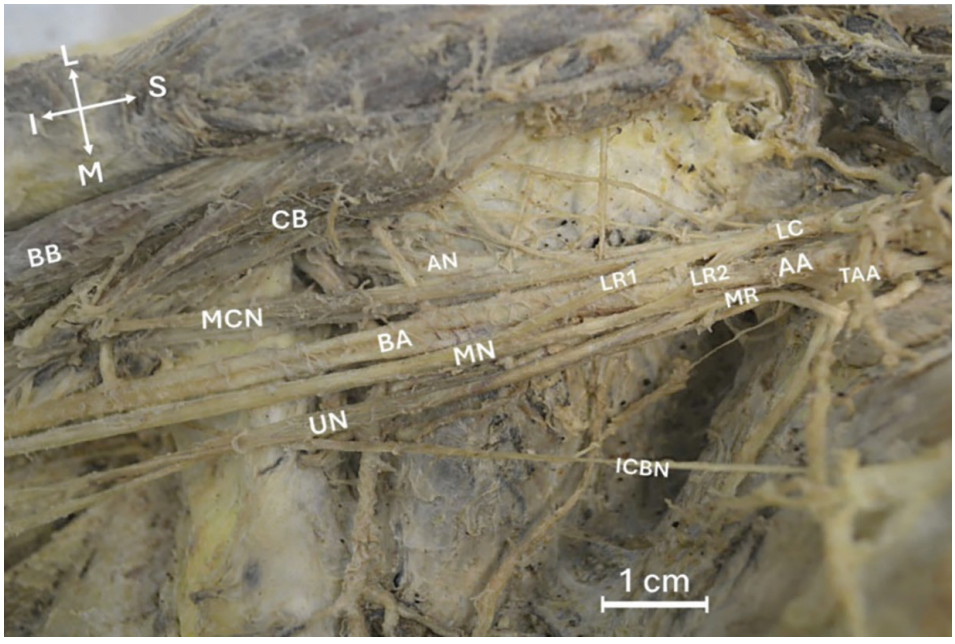

Figure 1. Anterior view of the proximal right upper limb demonstrating the formation of the median nerve (MN) by the union of its two lateral roots (LR1, LR2) and medial root (MR). The MN is shown immediately distal to its formation, in close proximity to the brachial artery (BA). The lateral cord (LC) of the brachial plexus gives rise to the lateral roots, while the axillary artery (AA) and thoracoacromial artery (TAA) are identified in the proximal region. The musculocutaneous nerve (MCN), ulnar nerve (UN), intercostobrachial nerve (ICBN), biceps brachii (BB), coracobrachialis (CB), and the axillary nerve (AN) are also labeled. Orientation markers indicate superior (S), inferior (I), medial (M), and lateral (L). Scale bar=1cm.

conditions. The site of nerve penetration and its intramuscular course are illustrated in Figure 3. This topographical variation was unilateral, while the musculocutaneous nerve, BA, and remaining neurovascular structures of the anterior arm compartment followed their typical courses.

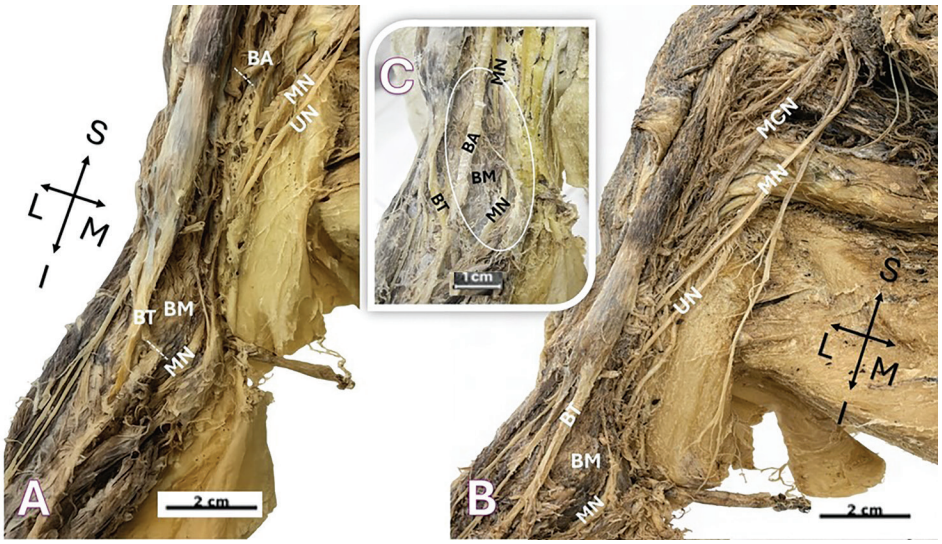

Figure 2. Panoramic anteromedial views of the right upper limb demonstrate an atypical intramuscular course of the median nerve (MN). (A) Proximal view showing the MN and ulnar nerve (UN) descending along the arm toward the brachialis muscle (BM). The brachial artery (BA) is transected (dotted line), and the bicipital tendon (BT) is identified for anatomical orientation. (B) Intermediate view illustrating the MN penetrating and traversing the middle third of the BM. The musculocutaneous nerve (MCN), UN, BT, and BM are labeled for reference. (C) Magnified view highlighting the point at which the MN enters and courses within the substance of the BM. BA and BM are shown in close relation to the intramuscular segment of the MN. Orientation markers denote superior (S), inferior (I), medial (M), and lateral (L). Scale bars=1 and 2 cm.

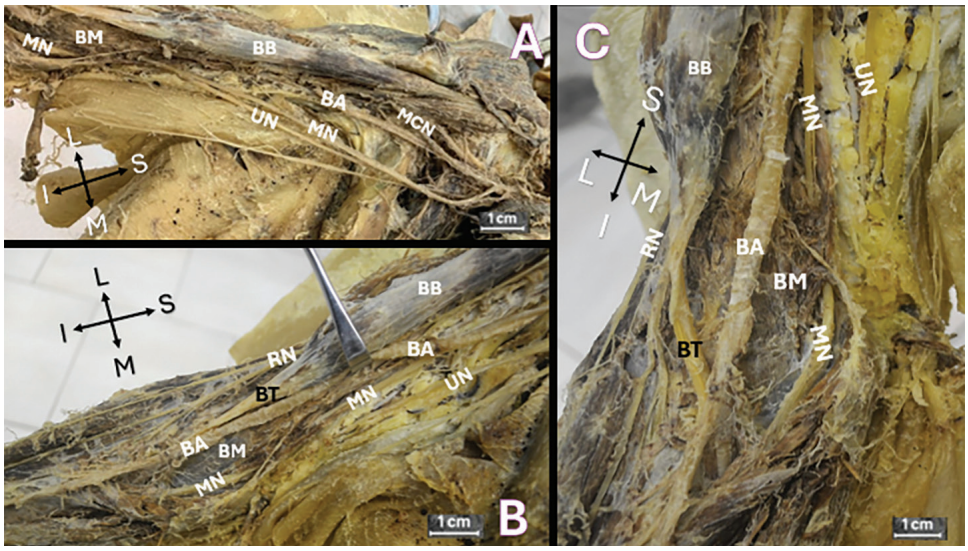

Figure 3. Composite views demonstrate the intramuscular segment of the median nerve (MN) within the brachialis muscle (BM). (A) Anteromedial view of the distal arm showing the MN and ulnar nerve (UN) before intramuscular penetration. The brachial artery (BA) is transected, and the musculocutaneous nerve (MCN) is identified in close relationship to the MN. The brachialis and biceps brachii muscles are evident (BM and BB). (B) Close-up view illustrating the MN traversing the BM. BB, UN, BT, BA, and the radial nerve (RN) are labeled for reference. RN is located lateral to BT. (C) Distal anterior view demonstrating the MN after emerging from the BM and reestablishing its superficial relationship with the BA. The BT, BB, UN, and RN are also identified. Orientation markers denote superior (S), inferior (I), medial (M), and lateral (L). Scale bars=1 cm.

Discussion

Abnormal courses of the MN in relation to the BM are rare. Bilecenoglu et al. (4) reported a cadaveric case in which the MN deviated from the BA and pierced the BM, while Loh et al. (2) and George and Nayak (5) described variants in which both the MN and BA traversed the BM within a common fascial sheath. Paraskevas et al. (1) documented an accessory MN branch piercing the BM and contributing to its innervation. In contrast, Barfi et al. (6) reported a case in which the MN passed deep into the BM. Additionally, Kumar et al. (3) described MN compression within an abnormal musculofascial tunnel formed by fibers of the BM and the medial intermuscular septum.

A distinguishing feature of the present case is the complete absence of MN innervation to the BM. Despite careful macroscopic examination, no motor or accessory branches were identified. This differentiates the present variation from previously described nerve-piercing configurations, in which intramuscular passage is frequently associated with supplementary muscular innervation (1, 4). The absence of a functional connection suggests a purely topographical deviation rather than a branching abnormality, a distinction that is clinically relevant because surgical decompression of the MN in this configuration would be unlikely to compromise BM function.

A developmental perspective may help explain the MN's atypical intramuscular course. During early upper-limb development (4^{th}–6^{th} gestational weeks), muscle primordia initially form as a premuscular mass and later differentiate through selective fusion and regression. Incomplete regression or atypical fusion of these primordia may result in persistent or aberrant muscle fascicles within the BM, potentially creating an abnormal intramuscular pathway. As peripheral nerves subsequently grow into the limb, their trajectories are influenced by surrounding developing muscles and connective tissue planes (7). Accordingly, an atypical brachialis fascicle could mechanically redirect the MN, explaining its deviation from the BA and intramuscular passage without associated motor innervation. In addition, developmental variations of the MN may reflect altered brachial plexus formation due to abnormal neuronal growth cone guidance and rearrangement of nerve fibers, influenced by adjacent developing muscles and vascular structures (8). Together, these mechanisms support a topographical developmental variation rather than a true functional branching abnormality.

Proximal MN irritation or compression at the arm level may produce symptoms that can resemble pronator teres syndrome, including forearm discomfort, muscle stiffness, clumsiness, and reduced grip strength, which may develop gradually or following repetitive activity or muscle strain (3, 9). However, no clinical correlation can be inferred from the present cadaveric findings. Prolonged nerve compression, when present, may lead to intraneural edema and progressive nerve dysfunction (10).

Entrapment neuropathies are generally attributed to chronic mechanical factors that may result in nerve deformation and impaired intraneural microcirculation. Although such mechanisms are most commonly described in association with musculofascial tunnels, the present case demonstrates an unusual configuration in which the MN courses directly through the BM. The surrounding muscle fibers closely encircled the nerve along its intramuscular segment, indicating a restricted anatomical corridor. Because cadaveric observations cannot replicate in vivo biomechanical conditions, it can only be suggested that contraction of the BM during elbow flexion might further reduce the available space around the nerve, potentially increasing intraneural pressure. This configuration may therefore represent a potential anatomical substrate for MN irritation or compression, particularly during repetitive or forceful elbow movements (3, 9, 10).

Diagnosis of proximal MN entrapment in the presence of anatomical variation may be challenging. Physical examination findings can be nonspecific, and electrodiagnostic studies remain essential for confirming the level of nerve involvement (11). Imaging modalities, including magnetic resonance

imaging and high-frequency ultrasound, may help identify anatomical relationships and dynamic nerve behavior (12, 13). Management of proximal MN entrapment typically begins with conservative measures such as activity modification and anti-inflammatory treatment (14). In cases where a direct intramuscular anatomical constraint is suspected, a shorter trial of conservative management may be appropriate. If surgical intervention is required, decompression may be achieved by carefully releasing the surrounding muscle fibers, as described for proximal MN decompression (15).

Conclusions

This case documents a rare anatomical variation in which the MN traverses the BM without contributing to its innervation. Such a configuration may represent a potential anatomical substrate for proximal MN irritation or compression. Awareness of this variation is important for surgeons, anesthesiologists performing regional nerve blocks, and clinicians interpreting imaging studies or evaluating unexplained MN neuropathies. This report underscores the importance of detailed anatomical knowledge in accurate diagnosis and safe clinical practice.

What Is Already Known on This Topic:

The median nerve (MN) usually follows a predictable course in the arm, descending in close association with the brachial artery (BA) and lying adjacent to, but not innervating, the brachialis muscle (BM). Although rare, anatomical variations involving the relationship between the MN and the BM have been documented. These include accessory MN branches supplying the BM, cases in which both the MN and BA traverse the BM, passage of the nerve through musculofascial tunnels formed by the BM and the medial intermuscular septum, and courses in which the MN lies deep to the BM. Such variants may predispose to proximal median nerve irritation or compression and may complicate surgical approaches, regional anesthesia, and imaging interpretation. Only rare cadaveric reports have described penetration of the BM by the MN following separation from the BA.

What This Study Adds:

This study documents a rare cadaveric variation in which the MN traverses the BM without providing motor innervation. Unlike previously reported variants, the intramuscular course in this case is purely morphological, without evidence of functional muscular supply. Such a configuration may represent a potential anatomical substrate for proximal MN irritation or compression and may clinically resemble pronator teres syndrome. In addition, this study provides insights into the anatomical basis of MN diagnosis and management. Awareness of this variant may improve diagnostic accuracy and help guide surgical procedures in the anterior compartment of the arm.

Authors' Contributions: Conception and design: GP and CL; Acquisition, analysis, and interpretation of data: GP, CL and MP; Drafting the article: CL, GT and AM; Revising it critically for important intellectual content: GP, CL, GT and AM; Final approval of the version to be published: GP, CL, GT, AM and MP.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Considerations: According to institutional guidelines, formal ethics committee approval was not required for this cadaveric study. All specimens were obtained through an accredited anatomical donation program, with informed consent provided in accordance with national and institutional ethical standards. Institutional approval was obtained for this cadaveric study. The corresponding ethical approval reference number is available upon request.

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Systematic Review
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Developmental Trajectories and Outcomes of Online Child Sexual Abuse: A Systematic Review of Longitudinal Studies

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Abstract

Background. OCSA includes adult grooming or solicitation and peer electronic sexual coercion. Due to its negative consequences, it has become a public mental health concern. While prevalence is well established, the developmental timing of onset, predictors, and outcomes can only be clarified through longitudinal studies. **Objective.** This review synthesizes longitudinal evidence on online child sexual abuse (OCSA) in minors, with an emphasis on developmental timing, prospective risk and protective factors, and downstream outcomes. Methods. A systematic review was conducted according to the PRISMA 2020 guidelines. Eligible studies enrolled participants under 18 years of age at baseline, used a longitudinal design, and examined OCSA. Twelve studies were identified through database searches (2000-2025) and citation chasing, all of which were published from 2013 onwards. Discussion. The narrative synthesis identified that the risk for OCSA was concentrated in mid-adolescence. Peer electronic coercion rose through early-mid adolescence and plateaued around the age of 16-17. The cumulative onset reached approximately one in three by age 18. The predictors included depressive symptoms, maltreatment, adverse childhood experiences, and risky digital behaviors. Protective parental monitoring buffered escalation, especially in early adolescence. In terms of consequences, adult solicitation predicted poorer quality of life and emotional distress, whereas peer coercion increased depression and delinquency. Bidirectional feedback loops emerged between adolescent sexting and adult solicitation. A school-based trial demonstrated that even brief prevention efforts can reduce the risk of OCSA. Conclusion. Longitudinal evidence suggests that OCSA follows an age-graded developmental pattern and is associated with potentially modifiable risk and protective factors. Prevention should focus on mid-adolescent hazard windows, minority-sensitive support, family-based monitoring, and digital safety education. The proposed Developmental-Online-Trajectories of Sexual abuse (DOTS) framework integrates these findings to guide future research, practice, and prevention.

Key Words: Online Child Sexual Abuse ▪ Grooming ▪ Electronic Sexual Coercion ▪ Adolescence.

Introduction

Digital technologies have reshaped the way young people connect with each other. Social and romantic interactions are now often tied to phones and platforms rather than to face-to-face contexts (1, 2). Adolescents spend long hours on messaging apps, social networks, gaming, or streaming, where many of them share pictures and videos every day (3-5). Some of these exchanges remain archived, others vanish instantly in stories, and algorithms silently decide who appears in their feeds (6, 7). In practice, private and semi-public online spaces often blur together. A chat may move across several apps, and images can be reshared or modified without consent (8). Child sexual abuse, as it has traditionally been studied, has involved the manipulation or coercion of minors for sexual purposes in offline contexts (9). Today, these harms also take on digital forms (10). Abuse may start online through grooming or sexual solicitation, involve pressure to share sexual images, or online contact can act as a gateway to an in-person meeting (11, 12). There are important differences between online and offline sexual victimization and related adverse experiences, including typical

perpetrator-victim dynamics, contexts of contact, and offense characteristics (13-16). However, they frequently co-occur and reinforce one another, so research and practice increasingly consider them together when assessing risk and impact (11, 12, 17-19). Online child sexual abuse (OCSA) is usually defined as the sexual exploitation, contact, or coercion of a minor through digital means, whether it remains online or later shifts offline (20-25). It primarily concerns situations in which adults or older adolescents target a minor for sexual purposes, in ways that meet legal thresholds for criminal behavior such as grooming, sexual extortion, or the production and distribution of child sexual abuse material (CSAM) (14, 20-26). The literature most commonly distinguishes two forms: (1) adult online grooming and sexual solicitation, which involve adult-child interactions, and (2) peer-perpetrated electronic sexual coercion, typically occurring within dating or romantic contexts (27-31). Thus, clear conceptual boundaries are essential, especially for distinguishing criminal or abusive adult-child interactions from other, sometimes normative, forms of sexual communication among peers. This review uses the 4C framework of content, contact, conduct, and contract (32) as a guide to sort these categories. OCSA should be separated from consensual sexting or general sexual exposure online, which can be linked to abuse but are not considered abuse alone (33, 34). Consensual peer sexting refers to voluntary, mutual exchanges of sexual messages or self-generated images between minors who perceive themselves as similar in age, power, and knowledge, and which may carry psychosocial risks but are not forms of abuse or criminal conduct (2, 33-35). In contrast, OCSA involves deception, coercion, pressure, or blackmail, or adult solicitation, possession, or dissemination of sexual content involving minors (14, 20, 24-26). Non-consensual intimate image (NCII) sharing and sexual extortion, including grooming, coercion, and threats to disseminate self-generated images unless a child complies, are forms of OCSA that are increasingly recognized in legal and policy responses (22, 23, 26, 35-38). At a global level, the problem of OCSA is a major cause for concern. In 2023 alone, over 36 million suspected OCSA cases were reported to hotlines (38). Reports have noted not only growth but also diversification, such as financial sexual extortion and AI-generated material (e.g., deepfake pornography) (38-40). A recent systematic review and meta-analysis estimated a past-year prevalence of 8.1%, with subtypes ranging from 3.5% for sexual extortion to 12.6% for non-consensual taking, sharing, or exposure to sexually explicit content (41). Routine activity theory (42, 43) provides a way to explain these dynamics. The risk is higher when adolescents encounter motivated offenders (e.g., when they befriend strangers), when guardianship is weak (low parental mediation), and when targets appear suitable (self-disclosure, risky self-presentation) (44). Moreover, it is also important to consider the developmental lens. Adolescence is marked by strong reward sensitivity, new social goals, and developing self-control (45-50). Taken together, these characteristics can make fast-paced digital interactions harder to manage, and resisting peer or adult pressure often requires considerable effort (27, 29). Research has linked several factors to a higher risk, such as being in mid to late adolescence, lower well-being, heavy Internet use, previous victimization, and risky self-presentation, including eroticized images (27, 51, 52). These vulnerabilities align with evidence that OCSA is associated with depression, anxiety, shame, reduced quality of life, and relational difficulties (12, 17, 18, 28, 53). In addition, sexual and gender minority youth show a higher prevalence of OCSA, partly due to prior adversity, bullying, and discrimination (8, 19). These insights clarify some patterns of onset and escalation. However, longitudinal research on adolescent OCSA remains scarce. Much of the literature is cross-sectional, terminology is inconsistent, and the geographic coverage is narrow.

Rationale for the Review

This review adopts a developmental perspective and synthesizes longitudinal research on OCSA in minors. Eligible studies examined adult online sexual solicitation or grooming, peer electronic

sexual coercion, online-initiated offline contact, and/or prospective outcomes and risk behaviors linked to OCSA. Consistent with recent terminology guidance, we included only studies addressing clearly abusive or exploitative online sexual interactions. Research on consensual peer sexting or general sexual exposure was retained only when it was explicitly tested as part of a pathway to OCSA. A longitudinal synthesis is warranted for three reasons. First, only longitudinal designs can resolve the temporal ordering of OCSA (29, 53, 54). Second, the literature has moved beyond single-wave prevalence to include survival, growth-curve, and cross-lagged models that can test bidirectionality (e.g., sexting and solicitation) and within-person change (33). Third, emerging intervention evidence suggests that trajectories can be altered through school-based prevention programs (55).

Thus, the main aim of this review is to synthesize longitudinal evidence on OCSA across childhood and adolescence, with an emphasis on temporal ordering and developmental timing.

Method

Based on a critical reading of the literature, five exploratory research problems were formulated to guide this synthesis. The first concerns the timing of OCSA onset, its persistence, and trajectory development across follow-up assessments. The second addresses prospective predictors of OCSA across individual, family, peer/school, and digital domains. The third focuses on prospective associations between OCSA and mental health, relational, academic, and risk outcomes, accounting for baseline adjustment. The fourth examines temporal ordering and potential bidirectionality between OCSA and co-occurring risks and behaviors, including offline victimization and risky online practices such as sexting, pornography use, and electronic harassment, across measurement waves. The fifth concerns heterogeneity in these patterns across key sociodemographic characteristics and OCSA subtypes. The aim is to integrate what longitudinal designs can reveal about timing and mechanism so that prevention and intervention can be directed to the right windows and targets.

Design and Search Strategy

This systematic review was guided by a pre-specified protocol that fixed the research questions, eligibility rules, and coding plan before screening. The review followed the PRISMA 2020 reporting guidelines, and the search was tailored to the field's fragmented terminology while remaining intentionally strict regarding study design (longitudinal only). The time window spanned January 2000 to August 2025, capturing both the pre-smartphone and smartphone eras. Core psychology, biomedical, and social science databases were searched, and this was supplemented by targeted additional sources (Google Scholar citation chasing and reference lists) to minimize the risk of missing relevant studies scattered across disciplines. Searches were limited to English-language publications only.

Inclusion and Exclusion Criteria

Studies were eligible if they (a) enrolled participants younger than 18 at baseline or reported adolescent-specific results separately, (b) used a longitudinal design with at least one prospective estimate (predictors of later OCSA, or OCSA of later outcomes), and (c) measured an OCSA construct aligned with this review's definition (adult grooming/solicitation, peer electronic sexual coercion, or clearly delineated NCII dissemination/sexual extortion/live-streaming/CSAM involving minors). Both antecedent (individual, family, peer/school, and digital factors predicting later OCSA) and outcome (OCSA predicting later mental health, relational/academic functioning, revictimization, or health risk outcomes) models were included. One-wave surveys, repeated cross-sections without within-person follow-up, purely qualitative research, measurement-only articles lacking longitudinal analyses, and samples in which adolescent data could not be isolated from adults (e.g., mixed-age panels without adolescent-specific estimates) were excluded from the scope.

Furthermore, studies that focused solely on non-coercive sexting or general sexual exposure were excluded, unless they were explicitly tested as part of the OCSA pathway.

Search Strategy

Because OCSA terms differ across disciplines, a combined controlled vocabulary was used for the search. The core string was: "online sexual" OR grooming OR solicitation OR sextort* OR "electronic sexual coerc*" OR "coercive sext*" OR "non-consensual intimate image*" OR NCII OR "cyber sexual abuse"* AND (adolescen* OR youth OR teen* OR child*) AND (longitudin* OR cohort OR prospective OR "follow-up" OR "cross-lag*" OR survival OR "growth curve"). The primary databases searched were PubMed/MEDLINE, APA PsycINFO, Web of Science Core Collection, ScienceDirect, ERIC, ProQuest, PsycARTICLES, PsycEXTRA, and Ovid MEDLINE. Furthermore, Google Scholar was searched with a 2000-2025 custom range, and forward/backward citation chasing was performed for all included articles. A PRISMA flowchart (Figure 1) documents the protocol used to conduct the current review.

Data Extraction and Analyses

A structured extraction template was piloted and refined, after which each study was coded for full citation, country, sample characteristics and age range, number of waves and inter-wave intervals, perpetrator type/abuse form (adult grooming/solicitation vs. peer electronic sexual coercion, with notes on NCII dissemination/sexual extortion and online-to-offline bridges), OCSA measurement, analytic approach (e.g., cross-lagged panel, latent growth, survival/Cox, mixed-effects, randomized trial models), antecedents/predictors and outcomes, and effect sizes with confidence intervals and covariate adjustments. To avoid double-counting, each study that used the same cohort was linked to the relevant research question it

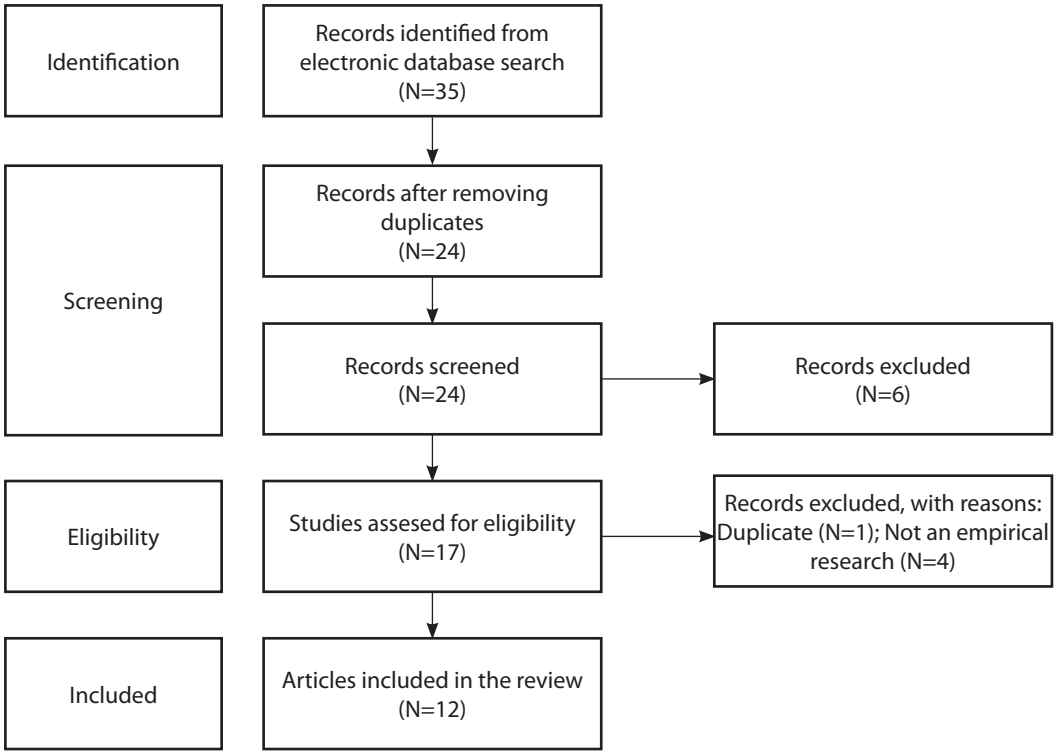


Figure 1. Flowchart of the article selection process based on the PRISMA guidelines (2020).

answered (e.g., onset/trajectories vs. mental-health outcomes). The risk of bias was assessed using the JBI Checklist for Cohort Studies (56), and the Cochrane RoB 2 tool was used to evaluate biases in randomized trials (57). All assessments were conducted by a single reviewer, guided by the official manuals and piloting of the tools to ensure consistency. Risk of bias ratings informed the interpretation of the evidence but were not used as exclusion criteria. These assessments were then used to inform the interpretation instead of excluding papers post-hoc. Owing to the considerable variation in conceptualization, measurements, and follow-up intervals, a meta-analysis was considered inappropriate. Instead, a structured narrative synthesis was carried out according to the SWiM guidelines (58).

Results

Study Selection

The search identified 11 records from databases (PubMed/MEDLINE = 3; PsycINFO = 3; Web of Science = 3; ScienceDirect = 2) and 2 from other sources (Google Scholar via citation chasing). After deduplication, 13 unique records were screened by title and abstract, after which one was excluded for focusing solely on non-coercive sexting without an OCSA pathway. Full texts were sought and assessed for all 12 articles, and all 12 met the eligibility criteria and were included in the synthesis (Table 1). No eligible longitudinal studies published before 2013 were identified. The final sample, therefore, reflects research conducted between 2013 and 2025.

Study Characteristics

The corpus comprised 12 longitudinal studies of minors, including those from Spain (17, 27, 28, 33, 55), the United States (8, 11, 12, 29, 53, 54), and Taiwan (59). Across these studies, the age range extended from late childhood to late adolescence (approximately 10–18 years). All included studies were published after 2013, despite the broader search window from 2000 onward. The designs included 2 to 4 wave panels (with a typical lag of 12 months), latent growth and survival models, one naturalistic cohort with objective web-trace data (8), and one school-based RCT with 3- and 6-month follow-ups (55).

Incidence and Developmental Course

Across peer-focused cohorts, electronic sexual coercion rose from early to mid-adolescence and then plateaued around ages 16-17 (latent growth; 29). In event-time analyses, the cumulative incidence of coerced peer sexting reached approximately 1 in 5 by age 15 and 1 in 3 by age 18, with the steepest increase in risk between the ages of 14 and 16 (54). For adult-initiated online sexual solicitation, a three-wave Spanish school cohort of 12- to 15-year-olds documented both new onsets and persistence of online sexual solicitation and sexualized interactions with unknown adults over a single school year (28). A separate two-wave Spanish cohort with a one-year interval found that grooming victimization remained stable for a subgroup of adolescents (17).

Prospective Antecedents

Risk accrued across developmental, psychosocial, and digital domains. Baseline depressive symptoms prospectively predicted subsequent adult-initiated sexualized encounters with minors (27). A history of maltreatment and early online risk behaviors predicted online sexual solicitations and encounters with individuals initially encountered online (11). In survival analyses, pornography use, electronic harassment, greater engagement in dating behaviors, and adverse childhood experiences (ACEs) predicted an earlier onset and increased risk of coerced sexting (54). In Taiwan's national cohort, gaming, exposure to pornography, engagement in broader risky Internet behaviors, depression, and involvement in cyberbullying (as victims and/or perpetrators) were predictors of victimization (59). Conversely, the use of chat rooms, exposure to pornography, engagement in risky Internet

behaviors, cyberbullying, and offline sexual harassment were predictors of perpetration (59). An observational study utilizing objective browser traces found high-risk digital behavior profiles that anticipated subsequent online sexual solicitations and cyber-victimization (8). On the protective side, higher parental monitoring was associated with a flatter growth in peer electronic sexual coercion, especially earlier in adolescence (29).

Outcomes Following OCSA

Prospective outcome models converged on mental health and functioning costs. Persistent or early adult solicitation and sexualized interactions predicted a lower health-related quality of life (HRQoL) at follow-up (28). The stability of grooming over a year forecasted higher depression, anxiety, shame, and guilt (17). Within-person panel models showed that peer electronic sexual coercion at baseline predicted increases in depressive symptoms and delinquency at follow-up, even after accounting for in-person dating violence (53). In a cohort linking online experience classes to later offline harm, an online-inclusive risk class predicted subsequent sexual assault and HIV risk behaviors, with stronger effects among maltreated youth (12).

Bidirectional and Cyclical Processes

Evidence for reciprocity is clearest for adolescent sexting and adult solicitation, with each predicting increases in the other over one year once baselines were controlled (cross-lagged panel; 33). The same study also found a feedback loop between sexting and cyberbullying victimization, suggesting that cycles of digital risk extend beyond sexual content and into broader online victimization. Another cross-lagged panel study modeled depressive symptoms and online sexual victimization reciprocally; however, the effects were strongest from symptoms to later victimization, with little support for the reverse once controls were applied (27). Within-person models of peer electronic sexual coercion likewise indicated directional rather than reciprocal processes, with coercion forecasting later depression and delinquency but not vice versa (53). Taken together, reciprocal pathways have been demonstrated for sexting and solicitation, and to a lesser extent for depression and victimization, while other longitudinal cohorts have primarily tested unidirectional risks.

Heterogeneity and Moderators

Several studies have tested the moderators of risk and persistence. Stable grooming victimization was more common among sexual minority adolescents and those with lower parental education, and stability was associated with greater emotional harm (17). Parental monitoring reduced the increase in peer coercion, exhibiting the most significant protective impact during early adolescence (29). ACEs hastened the initiation of coercive sexting (54), whereas maltreatment exacerbated the associations between online-inclusive profiles and subsequent sexual assault/HIV risk (12). Formal tests by sex/gender, disability, and area were infrequent, and when conducted, the patterns typically corresponded with the overall effects.

Period and Platform-Affordance Signals

Direct comparisons of pre-smartphone and post-smartphone cohorts or explicit tests of platform affordances in relation to OCSA were largely absent. Most studies inferred exposure from behaviors that reflected underlying affordances, for example, high-volume messaging, use of pornography, participation in chat rooms, or engagement in broader risky digital routines (54, 59). These measures capture adolescent engagement with features such as anonymity, accessibility, or constant connectivity; however, they do not isolate the affordances themselves. A notable exception was a naturalistic cohort study that combined objective web-trace data with follow-up interviews and demonstrated that high-risk browsing profiles forecasted later online sexual solicitations and victimization (8). Overall, the available evidence supports a link between everyday digital routines and subsequent

Table 1. Research Articles Included in the Systematic Review

Article	Method	Participants	Age range	Country	Main purpose
de Santisteban, Gámez-Guadix (2018)	2-wave school panel; cross-lagged paths over 1 year	Secondary-school adolescents	12-14 (M=13.11; SD=0.79)	Spain	Do internalizing symptoms forecast later adult-initiated online sexual solicitations/sexualized interactions?
Gámez-Guadix, Mateos-Pérez (2019)	2-wave school panel; cross-lagged models	Early adolescents	12-14	Spain	Test reciprocity between adolescent sexting and adult online sexual solicitation.
Ortega-Barón et al. (2022)	3-wave cohort across a school year (13 months)	School-based sample	12-15	Spain	Track onsets/persistence of adult solicitation/sexualized interactions and examine adjustment.
Gámez-Guadix et al. (2023)	2-wave cohort over 1 year	Adolescents	12-14 (M = 13.34; SD = 0.87)	Spain	Examine the stability of grooming victimization and emotional adjustment; test equity moderators.
Noll et al. (2013)	Prospective cohort; logistic regression	Maltreated girls and community comparison	14-17	USA	Do maltreatment and online behaviors forecast solicitations and online-to-offline meetings?
Noll et al. (2022)	Naturalistic cohort with objective web-trace data; ~2-year follow-up	Adolescent girls	12-16	USA	Identify high-risk digital behavior profiles and test whether they forecast later victimization.
Thulin (2022)	4-wave latent growth modeling (annual)	School-based cohort	13-18	USA	Map developmental trajectories of peer electronic sexual coercion and test protective factors.
Thulin et al. (2023)	Discrete-time survival/ Cox models across four years	School-based cohort	13-18	USA	Pinpoint age at onset and accelerators for coerced sexting.
Thulin et al. (2024)	4-wave random-intercept panel models	School-based cohort	12-18	USA	Test within-person effects of peer electronic sexual coercion on later functioning.
Calvete, Orue, Gámez-Guadix (2022)	School-based RCT with 3- and 6-month follow-ups	Adolescents	11-17	Spain	Evaluate a brief program to prevent online grooming.
Maas, Bray, Noll (2019)	Prospective cohort; latent class → outcomes over 1 year	Adolescent girls	14-17	USA	Do online-inclusive sexual experience profiles predict later offline harms?
Chang et al. (2016)	2-wave national school cohort; logistic/path models (1 year)	10th-11th graders (large national sample)	15-17	Taiwan	Identify predictors of unwanted online sexual solicitation (victimization and perpetration).

Perpetrator type / Abuse form	Waves / Lag	Predictors / Antecedents	Effect metric	Results
Adults soliciting/grooming minors online (sexualized interactions)	2 waves; 12 months	Depressive symptoms (T1)	β (cross-lagged)	Higher depressive symptoms at baseline predicted greater adult-initiated sexualized interactions one year later; reverse path ns after controls.
Adults soliciting minors online; adolescent sexting tracked as linked behavior	2 waves; 12 months	Sexting (T1) and solicitation (T1)	β (cross-lagged)	Bidirectional links: baseline sexting predicted later adult solicitation, and baseline solicitation predicted later sexting.
Adults unknown to the adolescent; online sexual solicitation/sexualized interactions	3 waves; 5 months (T1-T2), 8 months (T2-T3), 13 months total	Victimization pattern (early vs none)	aOR / β	Early/persistent victimization predicted lower health-related quality of life at follow-up.
Adults grooming minors online (repeated episodes)	2 waves; 12 months	Sexual minority status; parental education (moderators)	β / group contrasts	Stable grooming predicted higher depression/anxiety and shame/guilt; stability more likely among sexual-minority youth and those with lower parental education.
Online contacts (adult age not always specified); solicitations and offline meetings with someone first met online	2 waves; 12-16 months	Maltreatment; online risks at T1	aOR (logistic)	Maltreatment predicted solicitations and offline meetings; online-risk behaviors independently predicted offline meetings.
Unspecified online actors; online sexual solicitations/cybervictimization	2 waves (naturalistic); 24 months	High-risk digital behavior profiles (objective)	OR / β	High-risk objective profiles prospectively predicted later online sexual solicitations and cybervictimization.
Peers/dating partners; electronic sexual coercion (pressure, quid-pro-quo, threats)	4 waves; 12-month interval (annual)	Age (time-varying); parental monitoring; ACEs	Growth β (latent growth)	Coercion increased through mid-adolescence, plateaued ~16-17; higher parental monitoring buffered growth.
Peers/dating partners; coerced sexting	4 years (survival models); 12-month interval (annual)	Pornography use; e-harassment; dating behaviors; ACEs	HR (Cox)	Pornography use, electronic harassment, dating behaviors, and ACEs accelerated onset; risk concentrated in mid-adolescence.
Peers/dating partners; electronic sexual coercion	4 waves; 12-month interval (annual)	Coercion at time t	β (panel / RI-CLPM)	Electronic coercion at time t predicted subsequent increases in depression and delinquency (t+1), net of in-person dating violence.
Adults soliciting minors online; the outcome is sexualized interactions with adults when solicited	3 waves; Pre, 3-, 6-month follow-up	Intervention vs control	β / d (mixed models)	Intervention reduced sexualized interactions at 3-6 months and improved grooming knowledge versus controls.
Mixed online exposures (class includes online sexual risk; perpetrator age not disaggregated)	2 waves; 12 months	Class membership (T1)	OR / β	Online-inclusive class predicted later sexual assault and HIV-risk behaviors, with stronger effects among maltreated youth.
Victimization by online others (age not always specified); adolescent-perpetrated solicitation also measured	2 waves; 12 months	Gaming; pornography exposure; Internet risk; depression; cyberbullying	aOR / β	Victimization predicted by gaming, pornography exposure, risky Internet behavior, depression, and cyberbullying; perpetration predicted by chat-room use, pornography, risky behavior, cyberbullying, and offline sexual harassment.

OCSA risk, although it remains unclear which specific design features, including ephemerality, persistence, or algorithmic amplification, are the most influential.

Prevention Signals

One randomized trial in the set provided preliminary evidence of a preventive impact. Namely, a brief school-based prevention program reduced sexualized interactions with adults when solicited at 3-6 months and improved grooming knowledge relative to controls (55), indicating that near-term modification of risk is possible.

Risk of Bias Overview

Across the observational cohorts, the risk of bias was clustered in the confounding and follow-up domains. Thus, most studies used validated self-reports and appropriate longitudinal models (low risk for measurement/analysis); however, covariate adjustment was often limited, and attrition handling was variably detailed, yielding overall "some concerns" ratings. The randomized trial was overall low risk, with "some concerns" for missing outcome data and selective reporting, given the self-reported outcomes and incomplete pre-registration details. A brief summary is provided in Supplementary Table 1, with item-level JBI and RoB 2 in Supplementary Tables 2-3.

Discussion

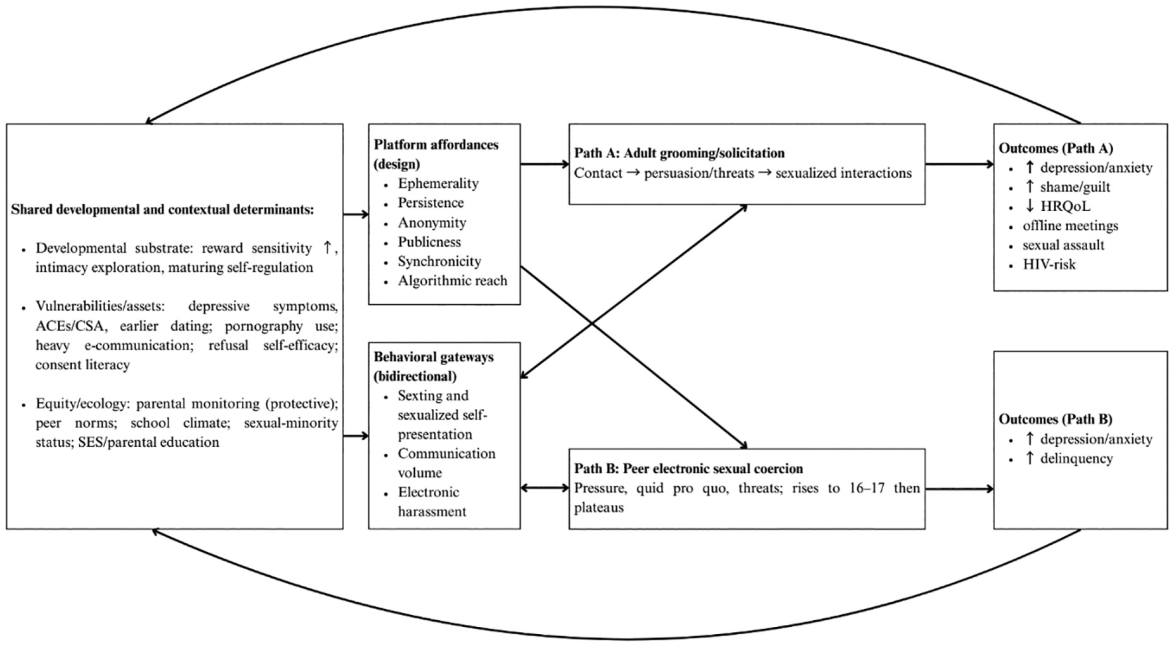
This review brings together longitudinal evidence on OCSA across childhood and adolescence. It traces when risks intensify, who is most vulnerable, and how harms unfold over time. To organize these findings in a coherent way, the Discussion draws on the proposed Developmental-Online-Trajectories of Sexual abuse (DOTS) model, a framework that groups developmental, digital, and outcome pathways.

The DOTS Model: Developmental-Online-Trajectories of Sexual Abuse

The proposed DOTS (Developmental-Online-Trajectories of Sexual abuse) conceptual model (Figure 2) offers a practical way to organize heterogeneous longitudinal findings without making strong causal claims. The model arranges evidence along four linked elements. It distinguishes shared determinants that shape vulnerability before an incident occurs, proximal digital processes that structure opportunity and leverage in everyday online life, two partially distinct trajectories that involve adult grooming and peer electronic sexual coercion, and downstream outcomes that can feed back into later risk. The purpose of this model is to provide a common vocabulary that allows studies using different measures and designs to be compared more directly while keeping the interpretation tied to longitudinal ordering rather than speculation.

Shared Developmental and Contextual Determinants

Middle adolescence appears to be a hazardous window in which reward sensitivity and social goal pursuit outpace still-maturing self-regulation, which is consistent with prior studies (46, 60). These age-graded hazards align with developmental accounts that emphasize rising social-reward sensitivity and intensifying peer orientation across mid-adolescence, which can heighten responsiveness to online social cues (48, 61). Furthermore, the evidence from this review is consistent with prior research showing that adolescents who report more internalizing symptoms are more likely to report unwanted online sexual solicitation or harassment, with effects especially pronounced among girls (62, 63, 64). In addition, high-risk youth show greater odds of receiving sexual solicitation and engaging in riskier contact behaviors (65, 66). Simultaneously, parental mediation is associated with lower exposure to sexual



Determinants (developmental factors, vulnerabilities/assets, equity/ecology) feed into platform affordances and behavioral gateways. These processes lead to two trajectories: Path A (adult grooming/solicitation) and Path B (peer electronic sexual coercion), culminating in adverse outcomes (mental health, HRQoL, and offline/relational harms). Dashed arcs indicate feedback loops from outcomes back to determinants. Arrows denote prospective associations, not causation; ACEs = Adverse childhood experiences; CSA = Child sexual abuse; HRQoL = Health-related quality of life; NCII = Non-consensual intimate images.

Figure 2. Proposed "DOTS: Developmental-Online-Trajectories of Sexual abuse" conceptual model.

risks and reduced harm when risks occur (5, 67). Finally, sexual and gender minority adolescents report markedly higher rates of online sexual harassment than their heterosexual peers, along with substantial distress (68). Together, these determinants interact with the design features of digital platforms, shaping how adolescents encounter and engage with specific online gateways that can open or constrain risk pathways.

Proximal Digital Processes: Platform Affordances and Behavioral Gateways

Sexting and sexualized self-presentation, high-volume online communication (especially with unfamiliar contacts), and electronic harassment operate as behavioral gateways that increase exposure to and normalize sexualized exchanges. The DOTS model separates platform features from the behaviors that bring young people into contact with risk because current evidence is uneven across these domains. Event-level affordances, such as ephemerality, publicness, persistence, anonymity, unsolicited contact, and the ease of forwarding or screenshotting, are theoretically central, but adolescent panels included in this review seldom measure them directly. Previous research has shown that publicness, persistence, anonymity, and low-friction contact widen exposure. Namely, EU Kids Online documents substantial sexual-message prevalence, and both the 4Cs framework and OECD guidance frame these as structural rather than purely individual risks (5, 32, 69). Moreover, earlier studies indicate that how teens use social media (e.g., in ways that are harmful to their health or that they feel they have to do) may be more important than how often they use it (61, 70). Research on platform affordances clarifies the mechanisms that may exacerbate vulnerability. Thus, features such as persistent streams, network

visibility, and low-friction messaging can heighten social comparison, exposure, and interaction with potentially harmful others (71).

The literature on behavioral gateways indicates that early offline sexual abuse is a particularly robust predictor of future OCSA, partly due to risky online behavior (19). Heavy communication and contacting strangers are associated with unwanted and more aggressive online sexual solicitations, as well as offline meetings (11, 72). Electronic harassment within dating contexts co-occurs with other forms of coercion and shows temporal coupling with in-person abuse, underscoring its gateway role (73, 74). An Australian survey linked image pressure and non-consensual forwarding to being female, online bullying, and prior sexual encounters (75). Therefore, OCSA is rarely an isolated incident but rather a component of the broader context of technology-facilitated sexual abuse (35, 76, 77). These interacting processes crystallize into two distinct trajectories of online child sexual abuse.

Two Trajectories That Can Bridge Online and Offline Contexts

In the DOTS framework, Path A captures adult grooming or solicitation. Adults, typically unknown to adolescents, initiate or escalate sexualized online contact. This pattern is linked to communication with strangers, high-contact platform use, and markers of psychosocial vulnerability (13, 65). Earlier evidence shows that such encounters are not rare and are associated with distress and poorer health-related quality of life (18, 28). Moreover, population surveys map sizable lifetime exposure to online grooming among youth and young adults, underscoring the public health relevance of this route (5, 14). Path B refers to peer electronic sexual coercion, which often involves known partners (14, 26). It is characterized by pressure, threats, or manipulation by same-age partners to obtain sexual images or interactions, often embedded in dating dynamics and broader cyber-dating abuse (2, 30, 31). Both trajectories can extend into youth's offline lives (15, 78, 79). The findings of this review are supported by previous research, which indicates different risk profiles for adult-perpetrated versus peer-perpetrated abuse (16, 78). In addition, these distinctive paths ultimately converge to a range of adverse health-related outcomes.

Downstream Outcomes

In the longitudinal corpus reviewed in this study, OCSA was followed by worsening mental health and functioning across both paths in the DOTS framework. Importantly, online risk is not hermetically sealed from offline harm. Adolescents who have experienced offline sexual abuse or maltreatment show elevated risk for online sexual solicitation and related victimization outcomes, and these harms often co-occur across settings (18, 19, 72). Beyond the longitudinal evidence reviewed here, international research and review studies report similar negative effects, with sexual extortion and image-based sexual abuse associated with increased depression, anxiety, and social or academic problems among youth (76, 80, 81). In addition, recent studies on youth sexual extortion indicate that it is highly prevalent and harmful to mental health, showing that sexual exploitation through technology is an increasing risk for youth (35, 36, 37). This aligns with previous findings linking image-based sexual abuse before age 18 to self-injury, suicide attempts, and drug overdose in childhood/adolescence (81). Furthermore, cross-sectional studies align with these findings, documenting worse psychological health among adolescents victimized online by offenders met on the Internet (18) and elevated distress associated with unwanted online sexual solicitation (64). In the DOTS model, these results are positioned on the right side of both paths to illustrate their convergence. The model also features feedback loops that show how cycles could occur. A negative mental state or relationship difficulties can make it harder to cope and may lead people to spend more time in higher-risk online areas, which can perpetuate the cycle in subsequent waves.

Limitations, Implications, and Recommendations for Future Research

Several limitations warrant caution when interpreting these findings. Studies are geographically concentrated (Spain, the United States, and East Asia), limiting generalizability to regions with different digital infrastructures and sex-education policies. Although the database search covered the period from 2000 to 2025, all eligible longitudinal studies were published from 2013 onwards. As a result, the conclusions primarily reflect OCSA in the contemporary, smartphone-dominated digital ecology rather than earlier internet eras. OCSA measures vary, and outcomes are often self-reported. Furthermore, attrition typical of school panels risks selective retention. Formal tests of period effects (pre- and post-smartphone cohorts) and platform affordances are scarce. Most evidence infers features from behaviors. Taken together, the findings should be interpreted with appropriate caution. Because this synthesis draws on observational longitudinal studies that vary in measurement precision, follow-up spacing, attrition, and adjustment for confounding, the inferences remain provisional rather than definitive estimates of risk, timing, or impact within a contemporary, smartphone-dominated digital ecology. Accordingly, the main patterns require further verification through replication in independent cohorts and triangulation across measurement approaches, ideally using more harmonized OCSA operationalizations and corroborating data sources beyond self-report (e.g., diary methods and objective digital trace indicators where feasible), alongside designs that more directly test competing developmental and causal explanations. Therefore, results from studies with stronger adjustment for confounding and lower attrition were afforded greater evidential weight, whereas findings from cohorts with higher dropout or weaker measurement strategies were treated more cautiously. This approach aligns with the current guidance, which recommends that risk of bias assessments be used to shape interpretation rather than to exclude studies after the fact (82). On this basis, three priorities follow from the DOTS model. First, perpetrator-specific measurements, including perceived power differences and relationship context. Second, research should specifically assess whether interactions occurred in ephemeral channels, anonymous spaces, public feeds, or permanent archives, and whether forwarding or screenshotting was used as leverage. Thus, research designs should combine survey, diary, and objective trace data to provide a more comprehensive methodological approach. Third, developmental resolution. Onset patterns suggest that shorter lags and age-based survival models may be particularly informative around transition points such as first smartphone access, first romantic relationships, and school transitions, especially when paired with within-person methods that separate stable between-person risk from within-person change (53). For practice and prevention, the longitudinal evidence supports targeting early secondary school and mid-adolescent hazard windows. Interventions may focus on refusal skills, emotion regulation under social pressure, and bystander responses, alongside parental guidance that emphasizes supportive, collaborative monitoring rather than purely restrictive control (29). At the program level, a brief school-based prevention reduced sexualized interactions with adults when solicited (55), demonstrating near-term prevention potential. Furthermore, active or restrictive media mediation is associated with lower odds of early adolescent sexting, reinforcing the role of family strategies in potentially risky online behavior (83). Parental mediation may also buffer downstream mental health impacts of online victimization, weakening longitudinal links between cyberbullying and later depression or self-harm (84). For youth with ACEs or histories of maltreatment, professional care might include digital safety planning that prepares them for the switch from online to offline spaces (11). Pediatric appointments could be useful for initiating a short conversation about youth digital routines in addition to regular topics. In addition to identifying groups at ongoing risk, such as sexual minority youth and those from resource-limited families, screening should focus on risk indicators that

consistently predict future exposure. Moreover, protective family processes should be implemented through an encouraging approach, including collaborative monitoring and transparent norms regarding privacy and consent (11, 17, 27, 29). Preventive advice about common ways that adults and peers try to coerce can be helpful, as well as practicing saying no and normalizing seeking help if an interaction feels forced. It is also beneficial to communicate a safety plan that includes information on how to report, block, and what to do if an image has been shared, including possible sexual extortion threats.

Conclusion

Longitudinal evidence indicates that OCSA increases and escalates primarily in mid-adolescence, is prospectively predicted by prior adversity and specific digital routines, and is followed by deterioration in mental health and behavioral outcomes. Adolescents with ACEs, sexual minority status, or lower parental education appear more likely to show earlier onset or greater persistence, whereas parental monitoring is consistently protective, particularly in early adolescence. Evidence for reciprocal links is strongest for the feedback loop between sexting and adult solicitation. Formal tests of platform-level affordances and period effects are limited, highlighting a measurement gap rather than a lack of association. The DOTS model synthesizes these strands into a developmental map with two perpetrator pathways, identifiable windows of onset and escalation, and interruptible feedback loops. The field now has the outlines of when and where to intervene. The next step is to pair higher-resolution measurements with multilayered prevention at home, school, pediatricians' offices, and on the platforms where youth spend significant amounts of their social lives.

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Appendix

Supplementary Table 1. Risk of Bias Summary by Domain for Included Studies (JBI for Cohort Studies)

Study	Selection of participants	Measurement of exposure	Confounding	Outcome measurement	Follow-up adequacy	Statistical analysis	Overall judgment
de Santisteban, Gámez-Guadix (2018)	Low	Low	Some concerns (limited covariates)	Low	Low (≈85% retention)	Low	Some concerns
Gámez-Guadix, Mateos-Pérez (2019)	Low	Low	Some concerns	Low	Low	Low	Some concerns
Ortega-Barón et al. (2022)	Low	Low	Some concerns	Low	Some concerns (attrition not fully addressed)	Low	Some concerns
Gámez-Guadix et al. (2023)	Low	Low	Some concerns	Low	Low	Low	Some concerns
Noll et al. (2013)	Low (prospective maltreated + comparison cohort)	Low	Some concerns (residual confounding likely)	Low	Some concerns (attrition reporting limited)	Low	Some concerns
Noll et al. (2022)	Low	Low (objective web-trace data)	Some concerns (residual confounding despite extensive covariate adjustment)	Low	Low	Low	Some concerns
Thulin (2022)	Low	Low	Some concerns	Low	Low	Low	Some concerns
Thulin et al. (2023)	Low	Low	Some concerns	Low	Low	Low	Some concerns
Thulin et al. (2024)	Low	Low	Some concerns	Low	Low	Low	Some concerns
Maas et al. (2019)	Low	Low	Some concerns (latent classes partly confounded by maltreatment)	Low	Some concerns (attrition)	Low	Some concerns
Chang et al. (2016)	Low (large national school sample)	Low	Some concerns (self-report depression only)	Low	Some concerns (attrition details limited)	Low	Some concerns

Supplementary Table 2. Item-Level JBI Risk of Bias Ratings for Cohort Studies (Q1-Q11)

Study	Q1*	Q2†	Q3‡	Q4§	Q5‖	Q6¶	Q7**	Q8††	Q9‡‡	Q10§§	Q11‖‖	Overall
de Santisteban, Gámez-Guadix (2018)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Gámez-Guadix, Mateos-Pérez (2019)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Some concerns
Ortega-Barón et al. (2022)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Some concerns
Gámez-Guadix et al. (2023)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Noll et al. (2013)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Some concerns
Noll et al. (2022)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Thulin (2022)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Thulin et al. (2023)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Thulin et al. (2024)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Some concerns
Maas et al. (2019)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Some concerns
Chang et al. (2016)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Some concerns

*Similar groups & same population; †Exposure measured similarly across groups; ‡Exposure measured validly/reliably; §Confounders identified; ‖Strategies for confounding; ¶Outcome absent at baseline; **Outcome measured validly/reliably; ††Follow-up time sufficient; ‡‡Follow-up complete / reasons explored; §§Strategies for incomplete follow-up; ‖‖Appropriate statistical analysis.

Supplementary Table 3. RoB 2 Domain-Level Risk of Bias Ratings for the Randomized Trial

Study	D1 Randomization process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall
Calvete et al. (2022)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns

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