OPEN ACCESS MACEDONIAN JOURNAL OF MEDICAL SCIENCES

oa mjms

eISSN 1857-9655

https://oamjms.eu/index.php/mjms

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Editorial Office

Scientific Foundation SPIROSKI, Rajko Zhinzifov No. 48, 1000 Skopje, Republic of Macedonia | Telephone: +389 70 255155. | e-mail: mspiroski@id-press.eu | URL: http://www.id-press.eu/mjms/

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 06; 14(1):1-6.
https://doi.org/10.3889/oamjms.2026.12108
eISSN: 1857-9655
Category: *G – Nursing*
Section: *Nursing in Internal Medicine*

Recognition of Dementia Symptoms and Related Work Challenges among Nursing Staff in Long-Term Care Facilities

Ljiljana Leskovic*

University of Novo mesto, Faculty of Health Sciences, Na Loko 2, 8000 Novo mesto, Slovenia

Citation: Leskovic L. Recognition of Dementia Symptoms and Related Work Challenges among Nursing Staff in Long-Term Care Facilities. Open Access Maced J Med Sci. 2026 Feb 6; 14(1):1-6. https://doi.org/10.3889/oamjms.2026.12108
Keywords: dementia; symptom recognition; long-term care; education; nursing staff; experience
***Correspondence:** Ljiljana Leskovic. University of Novo mesto, Faculty of Health Sciences, Na Loko 2, 8000 Novo mesto, Slovenia. E-mail: ljiljana.leskovic@uni-nm.si
Received: 14-Oct-2025
Revised: 15-Nov-2025
Accepted: 11-Dec-2025

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Recognition of dementia symptoms among nursing staff is essential for ensuring timely, person-centered and ethically adequate care. Despite an expanding global focus on dementia, evidence concerning the interaction between staff education, work experience, and their recognition competence in Central and Eastern Europe remains limited.

AIM: This study investigates the relationship between nursing staff's education and professional experience and their ability to recognize dementia symptoms, as well as their perceived work difficulty in providing care for residents with dementia.

METHODS: A cross-sectional survey was conducted among 104 nursing staff across three long-term care facilities in Slovenia. Data was collected using a structured questionnaire exploring recognition of dementia symptoms and perceived workload. Descriptive statistics, chi-square tests and logistic regression analyses were used.

RESULTS: Cognitive symptoms were recognized most accurately, while behavioral and emotional manifestations were less consistently identified. Education and work experience did not significantly predict perceived work difficulty.

CONCLUSIONS: Findings highlight the importance of strengthening behavioral symptom recognition through targeted education and institutional support mechanisms, rather than relying solely on staff experience or qualification level.

Introduction

Dementia, as one of the leading causes of dependency in later life, presents major challenges for long-term care systems globally [1], [2], [3]. The ability of healthcare professionals, particularly nursing staff, to correctly identify its cognitive, behavioural, and emotional manifestations is critical for the provision of person-centred care. Early recognition enables appropriate treatment, timely communication with families, and improved quality of life for residents [4], [5].

Although dementia care has received increased attention in Western Europe, evidence from Central and Eastern European (CEE) countries, including Slovenia, remains scarce. These healthcare systems often face workforce shortages, limited training opportunities, and structural fragmentation [6], [7], [8]. Consequently, symptom recognition in long-term care settings may depend not only on staff education and clinical experience but also on organisational culture and available institutional support.

Previous research has consistently demonstrated that education and ongoing professional training improve the accuracy of dementia symptom recognition [9], [10], [11], [12]. However, findings regarding the effect of years of work experience are mixed. Some studies suggest that experience increases clinical sensitivity [13], while others emphasise that repetitive routines and emotional exhaustion can reduce awareness of behavioural changes [14], [15], [16]. Furthermore, recognition ability

does not automatically translate into reduced work burden; stress perception is strongly influenced by workplace dynamics, staff-to-resident ratios, and emotional climate [17], [18].

In Slovenia, nursing staff in long-term care institutions represent the backbone of daily care provision. Yet their competence in recognising dementia symptoms has rarely been systematically investigated. Given the country's ageing population and the projected increase in dementia prevalence—from approximately 35,000 cases in 2020 to more than 60,000 by 2040—the need for evidence-based workforce strategies is urgent [19].

This study therefore aims to assess the ability of nursing staff to recognise prevalent dementia symptoms; examine whether staff education and years of experience predict perceived work difficulty; and identify potential areas for improvement in staff training and institutional support. By addressing these objectives, the study contributes to the limited regional literature and supports the development of national dementia strategies aligned with EU policy frameworks.

Materials and Methods

Study Design and Ethical Considerations

A quantitative, cross-sectional design was adopted to investigate relationships between staff characteristics and dementia-symptom recognition. Ethical approval was obtained from the Research Ethics Committee for Studies Involving Human Participants (Ref. No. 2024-112). Participation was voluntary, anonymous, and based on informed consent. Data confidentiality and the right to withdraw were assured in accordance with the Declaration of Helsinki.

Setting and Justification for Facility Selection

Data were collected in **three Slovenian long-term care facilities**, purposefully chosen to ensure **maximum variation** in terms of size, geographic region (central, eastern, and southern Slovenia), and organisational model (public, private, and mixed). The rationale for limiting the study to three institutions was methodological and ethical: (1) to achieve diversity while ensuring depth of contextual interpretation; (2) to secure feasibility given the limited availability of institutions granting ethical access for research; and (3) to maintain a manageable sample size for pilot-level statistical analysis. This design aligns with exploratory approaches used in small-country health-system research, where representativeness is achieved through institutional heterogeneity rather than sample quantity [20], [21], [22].

Participants and Data Collection

A total of 104 nursing staff participated, representing an estimated 80% response rate. Inclusion criteria were: (1) employment in direct resident care for at least six months, and (2) willingness to complete the survey during working hours. Exclusion criteria included administrative staff and temporary workers. Data were collected in November–December 2024 using self-administered questionnaires distributed through facility management.

Instrument

The survey instrument consisted of 15 items. Five questions covered sociodemographic data (gender, education, professional role, years of experience, and department). Ten items assessed recognition of dementia symptoms and perceived work difficulty, with responses measured on a 5-point Likert scale (1 = very low to 5 = very high). The items were based on previous validated instruments [23,24] and reviewed by three experts in geriatric nursing and cognitive disorders for content validity. Although the tool was not standardised psychometrically, its internal consistency was acceptable (Cronbach's α = 0.76).

Data Analysis

Data were analysed using IBM SPSS Statistics 29. Descriptive statistics summarised the sample characteristics. Associations between years of experience and departmental assignment were examined using Pearson's chi-square test. Logistic regression models tested whether education and work experience predicted perceived work difficulty. Statistical significance was set at $p < 0.05$. Results were presented in Tables 1–3.

Results

Participant Characteristics

Of the 104 participants, 88.5% were female. The largest group held secondary education (54.8%), followed by vocational (32.7%) and tertiary (12.5%) education. Regarding experience, 51.9% had ≤10 years, 26.9% had 11–20 years, and 21.2% had ≥21 years of service. Most respondents worked in nursing care units (55.8%), followed by dementia units (15.4%) and residential units (12.5%).

Table 1: Distribution of Participants by Department and Years of Experience

Years of Experience	Dementia Unit	Nursing Care	Residential Unit	Other	Total (%)
Up to 10 years	17 (15.4%)	30 (28.8%)	5 (4.8%)	2 (1.9%)	54 (51.9%)
11–20 years	8 (7.7%)	15 (14.4%)	3 (2.9%)	2 (1.9%)	28 (26.9%)
≥21 years	6 (5.8%)	13 (12.5%)	2 (1.9%)	1 (1.0%)	22 (21.2%)
Total	**31 (29.8%)**	**58 (55.8%)**	**10 (9.6%)**	**5 (4.8%)**	**104 (100%)**

Legend: χ^2 (9) = 8.656, p = 0.470. No statistically significant association between experience and department assignment.

Recognition of Dementia Symptoms

Recognition rates varied across symptom categories. As shown in Table 2, cognitive symptoms were recognised most reliably (88–92%), while behavioural and emotional indicators were less consistently identified. The lowest recognition was observed for the symptom "wants to go home," often misinterpreted as restlessness or noncompliance. This pattern suggests gaps in understanding behavioural communication among residents with dementia.

Table 2: Recognition of Dementia Symptoms by Category

Symptom Category	Symptom Example	Correct Recognition (%)
Cognitive	Does not recognise familiar people	92.3
Cognitive	Repeats phrases or questions	88.0
Behavioural	Wants to go home	64.4
Behavioural	Increased irritability or aggression	68.3
Emotional	Withdrawal or sadness	70.2

Legend: Data presented as percentage of respondents who correctly identified each symptom as indicative of dementia. Respondents could select multiple responses.

Perceived Work Difficulty

The average perceived work difficulty score was 3.4 (SD = 0.9), indicating moderate workload stress. Logistic regression analysis (Table 3) showed that neither education level nor years of experience significantly predicted perceived work difficulty ($p > 0.05$).

Table 3: Logistic Regression Predicting Perceived Work Difficulty

Predictor	B	SE	Wald	df	Sig. (*p*)	Exp(B)
Education level	-0.533	0.310	2.957	1	0.087	0.59
Years of experience	0.392	0.420	0.862	1	0.350	1.48
Constant	1.272	0.328	3.416	1	0.065	—

Legend: Model not statistically significant ($\chi^2 = 4.41$, df = 2, $p = 0.110$). Education and experience together explain approximately 6.3% of variance in perceived work difficulty (Nagelkerke $R^2 = 0.063$).

Discussion

The findings of this study confirm that while cognitive dementia symptoms such as memory loss and disorientation are reliably recognised by nursing staff, behavioural and emotional indicators remain insufficiently identified. These results are consistent with international literature, which suggests that staff often perceive behavioural expressions as personality changes or disruptive conduct rather than as manifestations of cognitive decline [25], [26], [27]. Behavioural symptoms, such as wandering, repetitive speech, or aggression, can also evoke emotional distress among caregivers, thereby influencing their perception of workload [28], [29].

The absence of a statistically significant relationship between education or experience and perceived work difficulty suggests that formal qualifications or tenure alone do not determine competence or resilience in dementia care. This aligns with research indicating that *situational* and *contextual* factors—such as team dynamics, emotional support, and management practices—play a more decisive role in shaping staff capacity [30], [31], [32].

In long-term care settings, routine exposure to residents with complex needs can normalise challenging behaviours, yet this habituation does not necessarily equate to better recognition or reduced stress. Rather, it can lead to *emotional desensitisation*, reducing sensitivity to subtle changes in behaviour that signal cognitive decline [33]. Such findings underscore the need for systematic emotional support and reflective supervision in institutional environments, ensuring that experience translates into clinical insight rather than fatigue.

Moreover, while education theoretically equips staff with diagnostic knowledge, its practical impact is contingent on ongoing reinforcement. Without continuous professional development, theoretical competence may deteriorate over time [34]. In Slovenia, as in many CEE countries, post-qualification training in dementia care remains sporadic, non-mandatory, and unevenly distributed across institutions [35]. Therefore, this study's findings can be interpreted as evidence of *structural limitations* rather than personal deficits among nursing staff.

Comparable studies in Western Europe, such as those conducted in the Netherlands, Sweden, and the United Kingdom, show that sustained investment in dementia-specific training programmes significantly improves staff competence and reduces perceived work stress [36], [37], [38]. For example, Dutch long-term care facilities implementing continuous education frameworks have reported higher recognition accuracy and lower turnover among care workers [39]. Similarly, in the United Kingdom, national dementia strategies have institutionalised training pathways that integrate both cognitive and emotional learning objectives [40].

In contrast, studies from Central Europe—Croatia, Hungary, and Poland—echo the challenges observed in this research: fragmented education systems, inconsistent standards of care, and limited access to supervision [41], [42], [43]. Thus, Slovenia's context mirrors broader regional patterns, where systemic rather than individual-level factors account for variability in staff competence.

These comparative insights underline the importance of national-level coordination to harmonise dementia-care standards, establish accreditation systems, and promote collaborative learning across care homes.

Organisational context strongly influences both recognition accuracy and perceived workload. Research consistently shows that supportive management, adequate staffing ratios, and participatory decision-making enhance staff well-being

and clinical performance [44], [45]. Conversely, hierarchical management structures and high staff turnover exacerbate burnout and diminish attentiveness to residents' psychosocial needs [46].

In this study, although no significant correlation was found between education or experience and perceived difficulty, qualitative feedback from participants (via optional comments) suggested that emotional burden and time pressure were primary stressors. Many respondents described a lack of opportunities for emotional debriefing after difficult shifts and limited managerial understanding of dementia-related challenges. This aligns with studies demonstrating that empathy fatigue can impede the accurate interpretation of behavioural symptoms [47].

The results lend partial support to the *Stress-Appraisal-Coping Model* (Lazarus & Folkman, 1984) [30], which posits that perceived stress depends not only on objective demands but also on individuals' appraisal of their resources and control. In this context, staff with similar educational backgrounds may perceive identical situations differently based on organisational culture, social support, and personal resilience.

From a theoretical standpoint, dementia care competence should be conceptualised as a dynamic interplay between cognitive knowledge, emotional intelligence, and organisational conditions. The present study contributes to this framework by empirically demonstrating that experience and education, while important, cannot compensate for systemic deficiencies in support structures.

The findings of this research have several practical implications for long-term care management and policymaking.

1. **Mandatory, continuous training:** Dementia-specific education should be integrated into ongoing professional development for all nursing staff. Periodic refresher courses focusing on behavioural and emotional symptom recognition would help sustain competence.
2. **Reflective supervision and peer support:** Implementing structured reflective sessions and peer discussion groups can mitigate emotional exhaustion, strengthen empathy, and improve recognition accuracy.
3. **Organisational leadership:** Managers should cultivate a learning-oriented organisational culture where staff feel supported to discuss care challenges openly without fear of blame.
4. **Standardised national guidelines:** Slovenia would benefit from adopting a national dementia-care training framework modelled after Nordic best practices, including certification and monitoring systems for long-term care institutions.
5. **Integration into public health policy:** Given demographic trends, dementia care should be recognised as a public health priority, with funding allocated to workforce development, staff retention, and interdisciplinary collaboration between healthcare and social services.
6. **Cross-border knowledge exchange:** Collaborations within the EU could enhance Slovenian institutional capacities through shared curricula, mobility programmes, and digital training platforms focused on dementia competence.

By addressing these aspects, policymakers can transform long-term care environments into learning systems that promote both quality of care and employee well-being.

Despite its relevance, this study has several limitations.

First, its cross-sectional design prevents causal inference. Longitudinal studies could better capture how experience and education influence recognition over time.

Second, the use of non-probability sampling and data from only three facilities limits generalisability. However, the selected institutions provided significant variation in structure and practice, enhancing interpretive depth.

Third, data relied on self-reports rather than observational measures, introducing potential bias. Future research could combine quantitative and qualitative approaches, including interviews and observational protocols, to triangulate findings.

Finally, the research instrument, though content-validated, lacked full psychometric testing; further studies should develop and standardise dementia-recognition scales for the Slovenian context.

Conclusion

This study underscores the complexity of dementia care within long-term institutional environments. While cognitive symptoms are generally well recognised, behavioural and emotional manifestations remain underidentified. Neither education level nor professional experience significantly influenced perceived work difficulty, highlighting the primacy of organisational and emotional support systems in shaping staff competence and resilience.

For Slovenia and similar healthcare systems, the implications are clear: effective dementia care cannot rely solely on the goodwill or experience of individual workers but must be embedded in structured, evidence-based, and institutionally supported frameworks. Continuous education, reflective

supervision, and cohesive teamwork should be prioritised as integral components of care delivery.

By documenting current strengths and shortcomings in staff recognition of dementia symptoms, this study provides a foundation for further national and international research. The results advocate for comprehensive dementia-care strategies that integrate clinical, organisational, and emotional dimensions, contributing to the long-term sustainability of care systems and the well-being of both residents and caregivers.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 10; 14(1):7-10.
https://doi.org/10.3889/oamjms.2026.12105
eISSN: 1857-9655
Category: *C – Case Reports*
Section: *Case Report in Internal Medicine*

Generalized Kaposi's Sarcoma in an HIV Negative Patient: Case Report

Entela Shkodrani[1*], Alert Xhaja[1], Dorina Ruci[2], Barbara Shkodrani[3], Dorina Billa[4]

[1]Clinic of Dermatology, University Hospital Center, Tirana, Albania; [2]Clinic of Rheumatology, University Hospital Center, Tirana, Albania; [3]Department of Medical Genetics, Preventive Biomedicine, University of Tor Vergata, Rome, Italy; [4]American Hospital, Tirana, Albania

Citation: Shkodrani E, Xhaja A, Ruci D, Shkodrani B, Billa D. Generalized Kaposi's Sarcoma in an HIV Negative Patient: Case Report. Open Access Maced J Med Sci. 2026 Feb 10; 14(1):7-10. https://doi.org/10.3889/oamjms.2026.12105
Keywords: Kaposi's Sarcoma; HHH-8; classic subtype; HIV/AIDS; IHC
***Correspondence:** Entela Shkodrani. Clinic of Dermatology, University Hospital Center, Tirana, Albania. E-mail: entela.shkodrani@gmail.com
Received: 5-Oct-2025
Revised: 14-Oct-2025
Accepted: 7-Nov-2025

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Kaposi's Sarcoma is a vascular neoplasm associated with human herpesvirus 8 (HHV-8). It typically manifests with cutaneous lesions but can also involve extracutaneous sites such as mucous membranes, lymph nodes and visceral organs. Kaposi's Sarcoma is classified in 4 major subtypes: classic, epidemic, endemic and iatrogenic. The classic form usually follows a slow course, with progressions of cutaneous lesions over more than 10-15 years. However atypical cases of this form have been described in the literature. We aimed to present an atypical case of generalized Kaposi's Sarcoma in an HIV negative patient.

CASE REPORT: We report an atypical case of Kaposi's Sarcoma (KS) classic type, in a 62-year-old HIV-negative male, notable for its unusual cutaneous presentation, distribution, and rapid progression. The patient presented to the Emergency Department with asymptomatic violet-to-red cutaneous lesions, including both plaques and nodules, distributed across the upper and lower extremities, abdomen, and back. The lesions first appeared approximately eight months prior but demonstrated a fulminant course in the weeks leading up to presentation, with rapid dissemination. Initial home management of the patient included local and oral folk remedies of unknown composition. A skin biopsy performed during hospitalization revealed nodular Kaposi's Sarcoma, and immunohistochemistry (IHC) was recommended for diagnostic confirmation. HIV serology was negative, and imaging, including lymph node ultrasound, revealed no evidence of visceral involvement.

CONCLUSIONS: This case illustrates an atypical presentation of classic Kaposi Sarcoma (KS) in an immunocompetent, HIV-negative patient, characterized by rapid progression and diffuse cutaneous involvement. Such a clinical course is uncommon for the classic subtype, which is typically indolent and slowly progressive. Our findings support the growing body of evidence that subgroups within classic KS may exhibit distinct clinical behaviors, requiring tailored staging and management strategies. Given the absence of any known immunosuppressive conditions or identifiable triggers, further research is needed to elucidate the underlying pathophysiological mechanisms in atypical cases of classic KS.

Introduction

Kaposi Sarcoma (KS) is a painless, angioproliferative spindle cell tumor originating from endothelial and immune cells infected with Human Herpesvirus type 8 (HHV-8) [1].

While it is most commonly known for involving the skin and mucous membranes, KS may also spread via lymphatic routes and affect internal organs, particularly in severe cases, with lesions appearing in the gastrointestinal tract and lungs. On the skin, it typically presents as a purplish-red macule, which may become confluent and elevated into plaques over time [2].

There are 4 subtypes of KS: classic, epidemic, iatrogenic and endemic. Each subtype presents with its own distinct characteristics regarding the morphology of lesions, time of onset, and pattern of progression. The classic form of KS typically follows a slow and indolent clinical course, often extending over 10 to 15 years or more. Lesions tend to appear and expand very gradually, usually beginning in the lower extremities, and the development of new lesions occurs slowly over time.

Case Presentation

A 62-year-old male from Tirana, was admitted to the Dermatology Department of the University Hospital of Tirana, as an emergency case in July 2024, following an 8-month history of disease onset. During this period, he had been treated with local and oral folk remedies of unknown composition. The cutaneous lesions were asymptomatic, appearing as violaceous to reddish in colour. Clinically, some presented as plaques, while others appeared as nodules. The lesions were widespread, involving the lower (Fig. 1) and upper extremities (Fig. 2), abdomen (Fig. 3) and back.

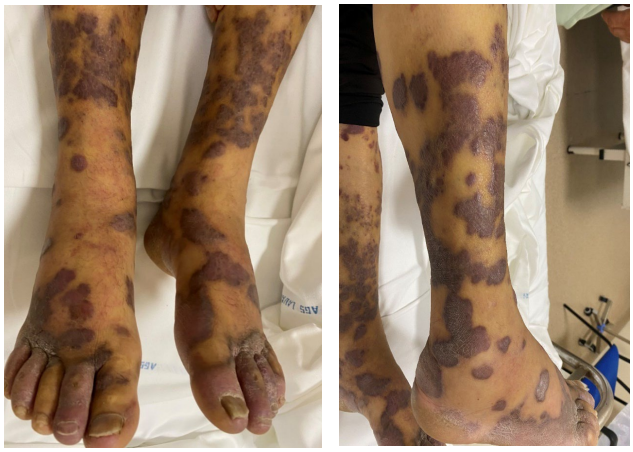

Figure 1: Red to violaceous macules, plaques and nodular lesions located in the lower extremities

The lesions demonstrated a rapid and widespread progression over a short period of time. Based on the clinical features, Kaposi Sarcoma (KS) was suspected, and a skin biopsy was performed for diagnostic confirmation. Histopathological findings included: a dermal spindle-cell proliferation arranged in vascular-like structures, showing moderate atypia and a low mitotic index, presence of mononuclear inflammatory infiltrates and siderophages (Fig. 4).

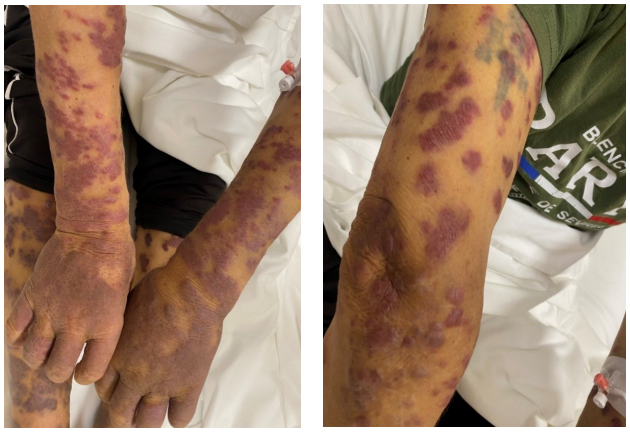

Figure 2: Red to violaceous macules, plaques and nodular lesions located in the upper extremities

This histopathological profile was suggestive of nodular-stage Kaposi Sarcoma. To confirm the diagnosis, immunohistochemical (IHC) analysis was recommended. The IHC results supported the diagnosis of KS and showed the following markers: Vimentin: positive, CD34: positive, CD31: positive, HHV-8: positive in endothelial cells, Ki-67: 10%.

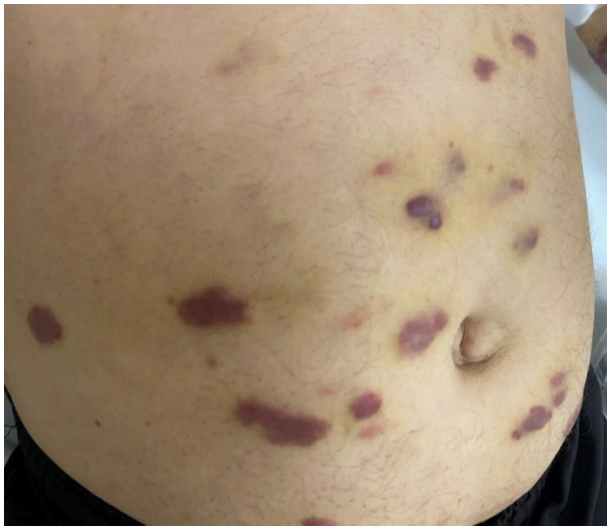

Figure 3: Kaposi lesions located at the abdomen

An ultrasound of the lymph nodes was also performed, revealing the following findings: non-reactive laterocervical lymph node (9 mm), supraclavicular lymph node on the left (8 mm), no paravascular adenopathy, reactive laterocervical (13 mm) and supraclavicular left (12 mm) lymph nodes, no right paravascular adenopathy. Not reactive axillary lymph nodes: left 18 mm, right 14 mm, no inguinal or para-aortic adenopathies bilaterally. Additionally, HIV testing was performed and returned negative. There was no evidence of visceral involvement.

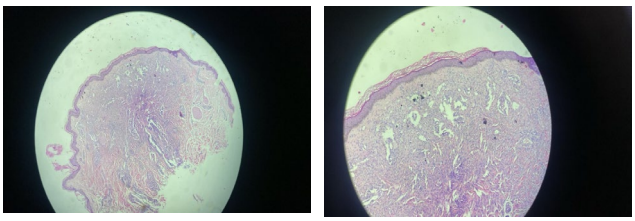

Figure 4: Dermal spindle-cell proliferation arranged in vascular-like structures, showing moderate atypia and a low mitotic index, presence of mononuclear inflammatory infiltrates and siderophages

The patient was referred to the Oncology Department for continuation of treatment. He underwent: 6 cycles of Doxorubicin (50 mg every two weeks), followed by 6 cycles of Paclitaxel (260 mg every two weeks). Compared to the previous CT there were no significant changes in the size of the laterocervical, mediastinal, or peri-aortic lymph nodes. However, infraclavicular left lymph nodes appeared reduced in size. Persistent cutaneous lesions were noted. Based on these findings, the patient was started

on a new treatment regimen with Vinblastine 10 mg, which he is currently continuing.

Discussion

Kaposi Sarcoma (KS) is a vascular neoplasm with both cutaneous and extracutaneous involvement. It is classified into four main clinical-epidemiological subtypes, each with distinct features in terms of lesion morphology, disease progression, and distribution [3], [4]. The classic subtype typically presents with slowly progressing nodules or plaques, most often located on the lower extremities, and primarily affects elderly men of Mediterranean origin. The endemic (African) form affects young adults and children in sub-Saharan Africa and may be locally invasive or involve visceral organs. Iatrogenic subtype occurs in organ transplant recipients receiving immunosuppressive therapy and often regresses after dose reduction or cessation. The epidemic (HIV/AIDS-related) subtype occurs predominantly in young men who have sex with men, with multifocal mucocutaneous lesions, rapid progression, and frequent visceral involvement [8], [9].

Although classic KS generally follows an indolent course over 10–15 years, atypical presentations have been increasingly reported. In our case, the patient demonstrated diffuse and rapidly progressing cutaneous lesions over a short period of time, without visceral involvement and HIV-negative status—a presentation not typical of classic KS. A study from the Department of Dermatology in Bari, conducted by Lospalluto, Mastrolonardo, Loconsole, Conte, and Rantuccio, proposed a classification of classic KS into three clinical subgroups based on cutaneous lesion dissemination. Their findings support the hypothesis that subgroups within classic KS exist, with distinct prognoses and treatment approaches [5]. According to this classification, our case corresponds to the HEG subgroup (High Extension and Growth), due to the rapid dissemination of lesions across multiple cutaneous regions. Another study from the Department of Dermatology in Istanbul, by Altunay et al., reported a rising number of clinically atypical KS cases [6]. For staging purposes, they utilized the Brambilla et al. classification (2003), which helps guide therapeutic decisions in classic KS [6]. Based on this system, our patient would be staged as classic KS, stage IVB.

One case in the Istanbul study involved an unusually aggressive course in a patient with classic KS, mimicking the epidemic (HIV-related) form clinically. This resembles our case as well, in which the diffuse cutaneous spread resembled a HIV-positive KS pattern, despite negative serology. In another case report from a Dermatology Department in Spain, a 52-year-old immunocompetent male with classic KS also presented with lesion characteristics typically seen in younger patients, adding further evidence for atypical variants of classic KS [7]. Notably, this patient reported same-sex sexual activity, a rare feature within the classic KS subtype, but more commonly associated with the epidemic form. This case report highlights the need for further investigation into the pathophysiological mechanisms that contribute to the development and progression of Kaposi Sarcoma in immunocompetent patients [7]. In our patient's case, the mechanisms underlying the rapid and diffuse cutaneous spread remain unclear. No identifiable etiological factor was reported during the clinical history that could explain such an aggressive course. The only possible contributing factor may be the use of non-medically supervised folk remedies, administered both topically and orally, with unknown composition. While a direct causative link cannot be confirmed, this highlights the importance of patient education and early referral to specialized care when skin lesions emerge.

Conclusion

This case illustrates an atypical presentation of classic Kaposi Sarcoma (KS) in an immunocompetent, HIV-negative patient, characterized by rapid progression and diffuse cutaneous involvement. Such a clinical course is uncommon for the classic subtype, which is typically indolent and slowly progressive. Our findings support the growing body of evidence that subgroups within classic KS may exhibit distinct clinical behaviors, requiring tailored staging and management strategies. Given the absence of any known immunosuppressive conditions or identifiable triggers, further research is needed to elucidate the underlying pathophysiological mechanisms in atypical cases of classic KS.

Additionally, this case underscores the importance of early dermatological evaluation and the potential risks associated with unsupervised alternative treatments in delaying diagnosis and appropriate care.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 12; 14(1):11-14.
https://doi.org/10.3889/oamjms.2026.12039
eISSN: 1857-9655
Category: *A – Basic Sciences*
Section: *Microbiology*

The Burden of Infections with Extended Spectrum Beta-Lactamase-Producing Pathogen on Home Health Care Services

Amjad S. Al Seraya* Kholoud Abdulaziz Bin Haikel

King Abdulaziz Medical City, King Abdullah International Medical Research Center, National Guard Health Affairs, Riyadh, Saudi Arabia

Citation: Al Seraya AS, Bin Haikel KA. The Burden of Infections with Extended Spectrum Beta-Lactamase-Producing Pathogen on Home Health Care Services. Open Access Maced J Med Sci. 2026 Feb 12; 14(1):11-14. https://doi.org/10.3889/oamjms.2026.12039
Keywords: outpatients' intravenous antimicrobial therapy (opat); antimicrobial resistance; multi-drug resistance; home health care; extended spectrum beta-lactamase (ESBL)
***Correspondence:** Amjad S. Al Seraya. King Abdulaziz Medical City, King Abdullah International Medical Research Center, National Guard Health Affairs, Riyadh, Saudi Arabia. E-mail: searyaa@mngha.med.sa
Received: 24-Feb-2025
Revised: 11-Sep-2025
Accepted: 5-Dec-2025

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Extended-spectrum beta-lactamase (ESBL) producing pathogens are a growing health threat due to their resistance to most of the commonly used antimicrobial agents.

AIM: In this paper, we aimed to assess the prevalence of those pathogens among patients who received care in the home parenteral antimicrobial therapy program. We also aimed to examine the burden of those pathogens on the home health care services and discuss the options to minimize this burden.

METHODS: This retrospective cohort study was conducted in the Adult Home Health Care Service at King Abdulaziz Medical City in Riyadh, Saudi Arabia. We studied all patients referring to the home health care parenteral antimicrobial program in the period from January 1, 2019 to December 31, 2021. Patients' data were retrieved from their electronic medical records. We classified patients as a patient with ESBL infection and a patient with a non-ESBL infection based on their cultures.

RESULTS: A total of 253 patients, of whom 144 (56.9%) were females, were accepted into the home parenteral antimicrobial therapy during the specified period. Of these, 121 (47.8%) were treated with an infection with ESBL-producing bacteria. Escherichia coli (92.76.0%) and Klebsiella pneumoniae (23.19.0%) were the most commonly isolated ESBL pathogens. Female gender, a previous history of UTI or ESBL infection, cognitive impairment and BPH in men were all associated with a higher rate of ESBL infections ($P<0.05$). Infection caused by ESBL-producing pathogen was not associated with a significantly increased rate of complications, readmission or mortality ($P\geq0.05$).

CONCLUSION: Almost half of the patients treated in the home parenteral antimicrobial program are infected with an ESBLproducing pathogens. However, we did not find any significant increase in adverse clinical outcomes associated with those infections in our sample. The burden on the HHC services that comes with these infections is mostly related to the limited choices of antimicrobials and to the high rate of recurrence.

Introduction

Extended-spectrum-beta-lactamase (ESBL) is a group of enzymes produced by some strains of gram negative bacteria, rendering them highly resistant to most of the commonly used antibacterial agents. As reported by the CDC, infections with ESBL-producing Enterobacteriaceae have been increasing since 2012 [1]. In its report for antimicrobial resistance threat in the United States, the Center of Disease Control and Prevention (CDC) classifies ESBL-producing Enterobacteriaceae as a "serious threat" and carbapenem resistant Enterobacteriaceae as an "urgent threat" [1]. In Saudi Arabia, a study conducted at a tertiary center in Riyadh examined 17,105 samples between 2006 and 2010 and reported 6.3% prevalence rate of ESBL-producing pathogens, mostly in urine samples [2].

Another report from the same period stated that 33% of urinary tract infections with Escherichia coli are caused by ESBL-producing E. coli [3]. A more recent study reported the prevalence of 67% of multidrug resistant E. coli and 33% of ESBL-producing E. coli in urine isolates [4]. This topic is relevant to home health care services today since they are dealing with those pathogens within their home antimicrobial programs. In this paper, we aim to examine this issue and its impact on care from the point of view of home health care specialists. We also try to investigate the role that the home health care departments can play toward the resolution of this current threat.

Materials and Methods

This retrospective cohort study was conducted in the Adult Home Health Care Service at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia. We studied all patients referred to the home parenteral antimicrobial program in the period from January 1, 2019 to December 31, 2021. We included all the accepted patients during this period. Patients' data were retrieved from their electronic medical record. The study was approved by the institutional review board of King Abdullah International Medical Research Center in KAMC (RYD-22-419812-128030).

The data were analyzed through SPSS software version 24.0 (NY: IBM Corp.). Continuous variables were presented as mean and standard deviation (mean ± SD), while percentages and frequencies were used to describe the categorical variables. The statistical analysis included Chi-square test that was used to measure the association between the two groups (the group with ESBL infection and the group with non-ESBL infection), the risk factors, and the clinical outcomes. P values less than 0.05 were considered statistically significant.

Results

As seen in Table 1, a total of 253 patients received therapy in the program during the identified period. Almost half of those patients were infected with an ESBL pathogen. Females were affected almost twice as much as males. The mean age of patients seen with ESBL was 75 years. Fifty-five percent of those patients were followed by HHC for other services.

Table 1: Patient Characteristics

Variable	ESBL	All
Female	ESBL: 77 (63.6%)	All: 144 (56.9%)
Male	ESBL: 44 (36.4%)	All: 109 (43.1%)
Total	ESBL: 121 (47.8%)	All: 253 (100%)
Age (Mean ± SD)	ESBL: 74.5 ± 13.8	All: 72.2 ± 15.5
Registered to other HHC programs	ESBL: 67 (55.4%)	All: 129 (51.0%)
Deaths	ESBL: 5 (4.1%)	All: 12 (4.7%)

Table 2 presents the risk factor and their association with having an ESBL infection. Female gender, a history of urinary tract infection (UTI), cognitive impairment, and benign prostatic hyperplasia (BPH) in males were significantly associated with having an ESBL infection.

Table 2: Risk Factors in Patients with ESBL Infections

Risk Factor	ESBL	All	P Value
Female gender	77 (53.5%)	144	0.04
UTI history	115 (55.6%)	207	0.00
ESBL history	98 (73.7%)	133	0.00
DM	89 (49.2%)	181	0.48
CKD	49 (54.4%)	90	0.12
Cognitive impairment	41 (57.0%)	72	0.07
BPH*	21 (60.0%)	35	0.00
Catheter*	10 (50.0%)	20	0.33

* For male patients only

As seen in Table 3, complications and mortality in both groups were similar; however, patients with ESBL infections had significantly higher rates of ER visits (p = 0.02).

Table 3: Complications in Patients with ESBL Infections During Therapy

Complication	ESBL	All	P Value
Complications	19 (42.2%)	45	0.41
Persistent infection	10 (52.6%)	19	0.66
Sepsis	3 (33.3%)	9	0.38
Readmission	31 (62.0%)	50	0.67
ER visits	40 (60.6%)	66	0.02
Deaths	5 (42.7%)	12	0.66

As shown in Table 4, E. coli and K. pneumonia were seen in over 90% of cases.

Table 4: ESBL Pathogens and Susceptibility

Pathogen	Frequency (%)
Escherichia coli	92 (76.0%)
Pan resistant (E.coli)	3 (3.3%)
Klebsiella pneumoniae	23 (19.0%)
Pan resistant (Klebsiella)	4 (17.4%)
Serratia marcescens	2 (1.7%)
Pseudomonas aeruginosa	2 (1.7%)
Enterobacter cloacae	1 (0.8%)
Morganella morganii	1 (0.8%)
Total	121 (100%)

Table 5 summarizes the diagnoses of patients with ESBL infections. Over 80% of our patients suffered from UTI or a urosepsis. Osteomyelitis was seen in 12% of patients.

Table 5: Diagnoses of Patients with ESBL Infection

Diagnosis	Frequency (%)
UTI	85 (70.2%)
Urosepsis	18 (14.9%)
Osteomyelitis	15 (12.4%)
Pneumonia	2 (1.7%)
Liver abscess	1 (0.8%)
Total	121 (100%)

Table 6 presents the antimicrobial agents that were used with those infections. Carbapenems (namely ertapenem and meropenem) were used to treat 90% of cases. Ceftazidime with avibactam and Tigecycline were used mainly in cases of carbapenem resistance.

Table 6: Antimicrobial Agents Used in ESBL Patients

Antimicrobial Agent	Frequency (%)
Ertapenem	92 (76.0%)
Meropenem	18 (14.9%)
Tigecycline	6 (13.2%)
Ceftazidime	5 (4.1%)
Total	121 (100%)

Discussion

Magnitude of the problem

During the period of 1/1/2019 to 31/12/2021, we have seen 119 patients (out of 253) with ESBL-producing pathogen infection that is proven by culture. Over 80% of those patients had a history of ESBL infection prior to this presentation. While receiving home care, 19 patients had complications and 20 had to be readmitted to the hospital. Three patients had sepsis while receiving home therapy, and 3 patients died. All ESBL patients had to be treated with parenteral antimicrobials, mainly ertapenem and

meropenem. However, a small, worrisome set of patients had a carbapenem resistant pathogen; therefore, IV tigecycline or ceftazidime/avibactam were used.

Burden of the Infection

ESBL patients represent almost half of the patients served by the HHC parenteral antimicrobial program. Those patients constitute a challenge to HHC on many levels. Current evidence suggests carbapenems to be the antimicrobial of choice for ESBL infections, owing to their effectiveness in treating the infection and their enhancement of survival rates [5]. Most of our patients were treated with either a course of ertapenem or meropenem. Ertapenem can be given once daily; however, it requires an infusion over 30 minutes, meaning longer HHC visits. Meropenem on the other hand is injected over 5 minutes, but requires multiple doses per day, mandating multiple daily visits. Challenges associated with carbapenems use include their parenteral route, high costs and susceptibility to resistance [6]. However, the duration of therapy is usually similar to the duration in non ESBL infections. Patients with ESBL infections have higher mortality and poorer outcomes compared to others infected with non-ESBL pathogens [7, 8]. ESBL patients are more likely to be hospitalized and to be admitted to ICU [9]. ESBL infections had been associated with severe infections as well as bacteremia [10]. Sepsis and bacteremia are feared complications that are associated with higher mortality [7, 8]. Recurrence of infection is also another factor that generously contributes to the burden of the infection [11].

Approaching the issue

HHC management of ESBL infections has been successful in treating patients with the added benefit of preventing transmission of infection to other patients as well as cutting the costs of management. Nevertheless, various measures can be taken to ensure the continuity of care and address this serious health threat on the level of HHC.

Preventive Measures

As in all cases of bacterial resistance, ESBL-producing bacteria thrive and evolve whenever antibacterial agents are misused. The implementation of antimicrobial stewardship (AMS) programs is vital to fight against the spread of ESBL infections. ESBL pathogens can also be transmitted through hands of patients and health care practitioners, which necessitates teaching patients, caregiver and HHC staff the importance of hand hygiene, especially when dealing with ESBL infected patients.

Decolonization therapy for patients who are carrier to ESBL pathogens is suggested to lower the infection rate and subsequently lower the morbidity and mortality rate without an increase in antimicrobial resistance [12]. However, data are still insufficient to recommend routine decolonization for patients carrying these pathogens [12].

Long-term nitrofurantoin has been prescribed to patients with recurrent ESBL infections; however, it carries a significant risk of toxicity and inducing resistance [13]. Fosfomycin and methenamine hippurate have been also used to prevent recurrent UTIs with some evidence supporting their effectiveness [7, 13]. Methenamine hippurate is specifically promising due to its safety profile and lack of resistance risk [7].

Addressing Risk Factors

Many risk factors for acquiring ESBL infections have been identified; however, the majority of them are non-modifiable. Risk factors include female sex, age older than 65 years, diabetes mellites, urinary catheterization, recurrent UTIs and prior administration of antibiotics [10]. Most of our patients have more than one of these risk factors, which might be a reason behind their high rate of recurrence. However, it is important to mention that patients without any of the documented risk factors might acquire the infection as well [7].

Early Initiation of Therapy

Many studies have investigated the impact of failing to provide sufficient antimicrobial therapy within 72 hours of infection on the patient's outcomes. A study described delay in early treatment as an independent predictor of death [14]. The length of delay in adequate treatment was also found to significantly increase the mortality rate and adverse clinical outcomes [7, 10, 14, 15]. It might be beneficial for the patient in HHC to have a system of dealing with patients with recurrent ESBL infections that can identify the infection and treat it early. Initiation of therapy by HHC has also the added benefit of preventing the spread of infection to the health care facilities and to the other hospitalized patients.

Use of New Technologies

Utilization of new technologies in HHC service might be a way to reduce costs and enhance patients' safety and satisfaction at home. One technology that can be used in the parenteral antimicrobial program is the 5 of 7 elastomeric infusion devices. Those devices, or pumps, can be easily operated by the patients or their caregivers without interfering with the patients' activities or sleep. They reduce the visits and the workload of the HHC staff, reduce the costs, and

enhance patients' satisfaction [16]. They can be specifically beneficial when administering a medication with frequent daily doses or a medication that needs to be administered over a long period of time.

Limitations

The limitation of the study is the comparison between the patients who required IV treatment for a significant infection and patients who had to be treated with IV antimicrobial agents merely for their susceptibility results - who might otherwise have been treated with oral agents and have not been referred to HHC services. This might result in underestimating the outcomes of an infection with an ESBL-producing pathogen.

Conclusions

Infection with ESBL-producing pathogens, acquired from the health care facilities and from the community, is on the rise. Home health care services are increasingly dealing with these infections and with patients carrier to these pathogens. The burden on HHC services from those infections is unlikely to subside, thus it is time for decision makers to think about the best strategies to lower this burden and provide the best care to the infected patients.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. King Abdullah International Medical Research Center (KAIMRC) issued approval IRB/1941/22. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 16; 14(1):15-19.
https://doi.org/10.3889/oamjms.2026.3072
eISSN: 1857-9655
Category: *B – Clinical Sciences*
Section: *Pediatrics*

The Influence of the Procalcitonin Method in Detecting Paediatrics Infections

Sani Bajrami[1,3*], Marika Mirkoska[2]

[1]Department of Neonatology, Department of Child, Clinical Hospital, Tetovo, RN Macedonia; [2]Department of Clinical Biochemistry, Clinical Hospital, Tetovo, RN Macedonia; [3]Faculty of Medical Sciences, Tetovo, RN Macedonia

Citation: Bajrami S, Mirkoska M. The Influence of the Procalcitonin Method in Detecting Paediatrics Infections. Open Access Maced J Med Sci. 2026 Feb 16; 14(1):15-19. https://doi.org/10.3889/oamjms.2026.3072
Keywords: bacterial infections; Procalcitonin; children
***Correspondence:** Sani Bajrami. Department of Neonatology, Department of Child, Clinical Hospital, Tetovo, RN Macedonia. E-mail: drsanibajrami72@gmail.com
Received: 16-May-2019
Revised: 10-Sep-2024
Accepted: 15-Dec-2025

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: In daily pediatric clinical practice, in addition to the standard markers such as PCR.

AIM: We aimed to demonstrate the role of Procalcitonin in early detection of bacterial infections of the respiratory tract at pediatric age and to determine the sensitivity, specificity, VPP, PCT VNP (quantitative method VIDAS-B-R-A-H-M-S-PCT) in bacterial respiratory infections.

METHODS: The prospective, randomized study, conducted at the Clinical Tetovo Hospital (Neonatology Department - Pediatric, Clinical and Biochemical Laboratory), in the period November 2011-December 2012. It includes 99 children. The study group includes 76 children. With upper respiratory tract infections (tonsil pharyngeal) 35 cases. With respiratory tract infections (bronchopneumonia) 41 cases, control group 23 cases.

RESULTS: With tonsil pharyngeal infections, out of 35 cases (28.57% were bacterial by criterion). With respiratory tract infections (bronchopneumonia), from 41s (39.02% were bacterial by criterion). In all 35 studies with bacterial tonsil pharyngeal disease, specificity, sensitivity, PPV, NPV of Procalcitonin, which resulted in the following (88%, 90%, 75%, 95.65%), and P = 0.12. All 41 patients with bacterial bronchopneumonitis were calculated as: Specificity, Sensitivity, PPV, and NPV of Procalcitonin, which resulted in the following (72.73%, 100%, 76%, and 100%). and P = 0.12.

CONCLUSION: Procalcitonin may serve as an early marker of upper and lower respiratory infections.

Introduction

With the term infectious bacterial disease, we mean pathological conditions directly caused by a certain number of microorganisms responsible for causing the disease.

Infectious respiratory diseases in childhood are frequent occurrences and account for about 70% of the general morbidity in childhood [1]. Pneumonia is a common disease affecting about 450 million people a year in all parts of the world [2], [3].

Acute tonsil pharyngeal - Commonly the inflammatory process affects tonsils and pharynx together, t tonsils and pharynx are commonly associated with tonsil pharyngeal diseases.

Many authorities recommend the use of 4 criteria for the diagnosis of pharyngeal tonsil, as follows: Fever, Tonsils with Exudates, Cough, and Cervical Anterior Lymphadenopathy. Patients who meet the 2 criteria can be tested [4] for Epidemiological survey; - Laboratory research; and Other research [5].

Blood analysis: Leukocyte differential leukocyte formula is very important for some diseases, especially for those with infectious origin. [6] Neutrophils- Neutrophilia indicates left-leukocyte leukocyte. Most often occurring in bacterial infections, tissue necrosis, we normally have also increased number of leukocytes [7], [8].

The role of procalcitonin in respiratory infections

Procalcitonin is a precursor of the calcitonin hormone, which is part of calcium homeostasis. It is composed of 116 amino acids, Fig. 1, and is produced by the thyroid (C-parafollicular) cells and the neuroendocrine cells of the lungs and intestines. Under

inflammatory systemic conditions, inflammatory mediators cause procalcitonin production in many places, from neuroendocrine cells throughout the body.

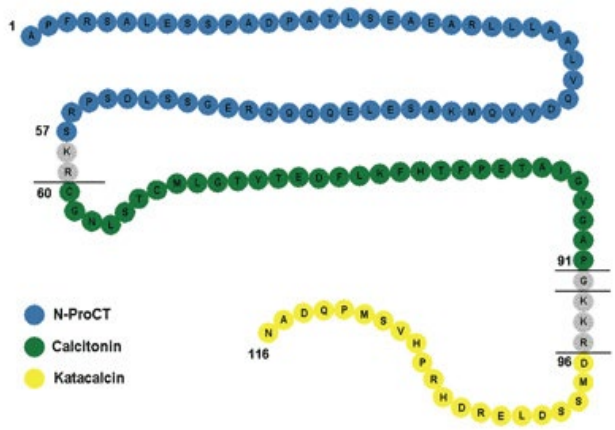

Figure 1: Primary Structure 116-kD Precursor Polypeptide of Calcitonin. The PCT composition of 116 amino acids produced by cells (C-parafollicular cells) of the thyroid and from the neuroendocrine cells of the lungs and intestines. Procalcitonin is composed of three sections: the amino terminus (N-ProCT), immature calcitonin, and katacalcin

Calcitonin discontinued procalcitonin was discovered in 1980. Ten years later, researchers found that procalcitonin levels increase in the presence of pneumonia, sepsis, or other bacterial systemic infection. Procalcitonin serum has a half-life of 25-30 hours [9]. The elevated levels of PCT show bacterial infection accompanied by systemic first published study that suggested that procalcitonin levels were increased in the presence of bacterial infection occurred in France in the early 1990s. A major advantage of PCT compared to other parameters is its very early growth and quite specific in response to severe systemic bacteria [10], [11], [12], [13], [14].

Trials from 2008 and 2009 have shown that procalcitonin may help guide therapy and reduce the use of antibiotics, which can help maintain the cost of using antibiotics and bacterial resistance [15], [16]

The purpose of this study is: 1. To reflect the role of Procalcitonin in early detection of respiratory infections at pediatric age; and 2. Recommend the role of Procalcitonin as an early biomarker in differentiating infections, in order to reduce daytime hospital stay.

Material and Methods

The study is prospective and randomized; 99 children were included in the study. The study lasted two years from November 2011 to December 2012 year. The clinical part of this study was carried out in Neonatology Departments and Children's Department at IPSH - Clinical Hospital Tetovo, Faculty of Medicine - USHT. The laboratory part was performed in the Clinical Biochemistry laboratory near the Tetovo Clinical Hospital. The men resulted 56 or 56.56%, females 43 or 43.43%. Average age 2.47 years ± 3.5 months, average length 81.42 ± 12.4 cm, mean hospital stay was 4.1 ± 1.3 days, mean weight 12.05 ± 2.8 kg, Diagnosis is based on data:

1. Clinical (auscultatory phenomena, local tonsil aspect, febrile condition, etc.)

2. Biochemical Examinations (Quantitative method of PCT (VIDAS-B.R.A.H.M. S PCT) cut-off > 0.25 ng/ml.

We divided the subjects into two groups as follows: 35 cases with acute tonsillopharyngitis, and 41 cases with bronchopneumonia. All 76 cases are diagnosed according to the criteria, with upper and lower respiratory tract infections (acute tonsillopharyngitis, bronchopneumonia), and 23 cases as a control group. Study group included 76 cases suspected of upper respiratory tract infections [ITSR] - acute tonsillopharyngitis and lower respiratory tract infections [ITPR], bronchopneumonia with clinical shyness in suspicion of respiratory infections in the presence or absence of infectious factors. The control group which consists of 23 cases that are occasionally selected without clinical signs and anamnestic for respiratory infection. All the examinations were performed as in the study group.

Results

The results are compared in the ratio between procalcitonin (PCT) and C reactive protein (CRP) and differentiated according to the etiology of infection. - In Upper respiratory tract infections [ITSR] - Acute tonsillopharyngitis.

The diagnosis is based on: presence of fever, changes in tonsils, lack of cough, cervical front lymphadenopathy. For the diagnosis of infections, we are based on findings such as: PCT, CRP, Le (neutrophil, lymphocytes), cramps.

According to etiology tonsillopharyngitis we have classified into:

- Bacterial: 10 or 28.57%, viral: 18 or 51.42%, unknown etiology 7 or 20% Out of a total of 35 cases, PCT increases to 12 or 34.3% of cases. CRP increased to 42.9%, in 77% increased number of leukocytes, increased lymphocytes at 68.6%, neutrophils in 31.42% of cases, the presence of local changes in tonsils at 88.57%, the cervical lymph glands in excess of 37.1%, coughing is not present at 45.7%, fetal condition in admission at 87.9%, positive strike in 17.14 cases.

- In respiratory tract infections [ITPR] – bronchopneumonia. The diagnosis of pneumonia was

based on findings: radiography and fever (> 37.5°C), respiratory phenomena, radiological diagnosis was done by independent radiologists and pediatricians, for the differentiation of infections we were based on findings such as PCT, CRP, Le (neutrophile, lymphocytes), aspirate tracheal. According to bronchopneumonia etiology we have classified: bacterial: 16 or 39.02%, viral: 9 or 21.95%, atypical 6 or 14.63%, unknown etiology10 or 24.39%.

Of the 41 cases, PCT increases to 26 or (63.4%), CRP to (34.1%), increased leucocytes at 75.6%, neutrophils increased to 46.34%, lymphocytes increase in 53.7%, out of 53.65% of patients with positive bronchopneumonia radiography, resulted in 63.63%, at 65.9% coughing present, febrile condition in admission in 75.6% of cases, and positive aspirations at 17.03%.

In the control group: Of the 23 cases, slight increase in Procalcitonin is found in 4 cases and in three cases in the newborn, which has not been significant for respiratory infections.

Children with tonsillopharyngitis

In patients with tonsillopharyngitis disease at 12 or 34.4% of patients showing increases in the value of the procalcitonin, 23 or 65.7% were with normal values of procalcitonin, the mean procalcitonin value was 1.73 ng/ml (Table 1).

Table 1: Percentage distribution by procalcitonin value in tonsillopharyngitis patients

Procalcitonin ng/ml	Number	Value in Percent
Patients with normal value (up to 0.25 ng/ml)	23	65.7%
Patients with values above normal (> 0.25 ng/ml)	12	34.3%
Total:	35	**100%**
The average value of procalcitonin in all patients	1.73 ng/ml	

In all 35 studies with bacterial tonsillopharyngitis disease, specificity, sensitivity, PPV, NPV of procalcitonin, which resulted in the following (88%, 90%, 75%, 95.65%), and P = 0.12.

Procalcitonin (PCT):
Sensitivity 90%
Specificity 88%
PPV 75%
NPV 95.65%
P = 0.12

Patients with bronchopneumonia

In patients with bronchopneumonia at 26 or 63.4% of patients showing PCT increase (cut-off > 0.25 ng/ml), 15 or 36.6% are of normal PCT values, the PCT average value were 6.61 ng / ml (Table 2).

Table 2: Percentage distribution of patients according to the value of procalcitonin, in patients with bronchopneumonia

Procalcitonin	Number	Value in Percent
Patients with normal value (up to 0.25 ng/ml)	15	36.6%
Patients with values above normal (> 0.25 ng/ml)	26	63.4%
Total	41	100%
Mean	6.61 ng/ml	

In all 41 patients with bacterial broncho-pneumonia, the following were calculated: Specificity, Sensitivity, PPV, NPV of procalcitonin, which resulted as follows (72.73%, 100%, 76%, 100%). and P = 0.12.

PCT:
Sensitivity: 100.00%
Specificity: 72.73%
PPV: 76.00%
NPV: 100.00%
P= 0.12

Statistical processing in the control group

In a studied control group of patients, leukocytes, lymphocytes, neutrophils, procalcitonin, CRP Tek 6 or 26.1% of patients showed a slight increase in the value of procalcitonin and in three cases in the newborn, 17 to 73.9% normal, the average PCT percentage in the patients studied as a control group was 0.28% (Table 3).

Table 3: Percentage distribution of patients as percentage of procalcitonin in patients as control group.

Procalcitonin	Number	Value in Percent
Patients with normal values(< 0.25 ng/ml)	17	73.9%
Patients with values above normal(> 0.25 ng/ml)	6	26.1%
Total	23	100%
Average value of lymfocits in all patients	0.28 ng/ml	

Discussion

Based on the results in both diagnoses of acute tonsillopharyngitis and bronchopneumonia PCT, CRP, Neutrophils have resulted in:

PCT:
Sensitivity: 95 %
Specifity: 80.36%
PPV: 75.5%,
NPV: 97.82%

CRP:
Sensitivity: 74.41%,
Specificity: 78.00%
PPV: 63.39%
NPV: 84.15%

Neutrophile sensitivity 90.57%, specificity 82.11%, PPV 77.92%, NPV 92.35%.

Which confirms the highest PCT values as compared to CRP and neutrophils in pediatric respiratory infections.

In all 35 studies with acute bacterial procalcitonin tonsillopharyngitis disease, the results were: Sensitivity, Specificity, PPV, NPVs below (90%, 88%, 75%, 95.65%) and P = 0.12. In all 41 patients with proximal bronchial bronchopneumonia disease resulted in: Sensitivity, Specificity, PPV, NPVs below (100%, 72.73%, 76%, 100%) and P = 0.12. According to the study our percentage of bacterial infections according to the criteria for diagnosis of bacteria based on the growth of PCT, CRP, leukocyte-neutrophils, lung radiography, acute stroke auscultative phenomena, febrile condition, is presented in these values:

- bacterial infections of the upper respiratory tract at 28.57%;
- bacterial infections of the respiratory tract at 39.02%.

As a result of the early detection of infections according to their etiology, it is possible to reduce antibiotic delivery, reduce day of stay or exclude the need for hospitalization.

Although this method has its own difficulties due to the high cost, it should be noted that from studies conducted by other authors, as it results from our study, the benefits are very large for patients as well as for health institutions having consider the rational use of antibiotics to be used in hospitals and shortening the days of attitudes in them.

Therefore, early and accurate diagnosis of bacterial infections is feasible at pediatric age using the procalcitonin method in order to prevent unnecessary administration of antibiotics or the same not to be initiated at all.

Conclusions

a) In our study PCT has resulted in 95% sensitivity, 80.36% specificity, PPV 75.5%, 97.82% NPV. Which confirms high PCT reliability compared to CRP and neutrophils in pediatric respiratory infections.

b) In all 35 patients with acute bacterial tonsillopharyngitis disease Procalcitonin resulted in: Sensitivity, Specificity, PPV, NPV (90%, 88%, 75%, 95.65%) and P = 0.12.

c) In all 41 patients with bacterial bronchopneumonia, procalcitonin resulted in: Sensitivity, Specificity, PPV, NPVs below (100%, 72.73%, 76%, 100%) and P = 0.12.

e) With high statistical value we can conclude that in our study PCT has resulted with 95% sensitivity, 80.36 specificity, 75.5% PPV, 97.82% NPV (p = 0.12) and difference between study group and the control group is of high statistical significance (p = 0.003). This correlation or statistical link is significant, i.e. important (p = 0.003).

Recommendations

1) Although this method has its own difficulties due to the high cost of procalcitonin reagents, the benefits are great:

- Reduce daytime hospitalization and rational use of antibiotics

2) Openness to further studies opens, as a new database of pediatric fields has been established, from clinically proven and diagnosed patients.

3) Establish the database of these data in the form of computer,

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 26; 14(1):20-32.
https://doi.org/10.3889/oamjms.2026.12051
eISSN: 1857-9655
Category: *F – Review Articles*
Section: *Narrative Review Article*

Age-Related Changes in Energy Expenditure

Nikolay Botushanov[1], Aleksandar Botushanov[1], Albena Botushanova[2]

[1]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria; [2]Department of Clinical Oncology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria

Citation: Botushanov N, Botushanov A, Botushanova A. Age-Related Changes in Energy Expenditure. Open Access Maced J Med Sci. 2026 Feb 16; 14(1):15-19. https://doi.org/10.3889/oamjms.2026.12051
Keywords: Aging; Energy Expenditure; Resting Metabolic Rate; Thermic Effect of Food; Non-Exercise Activity; Thermogenesis
***Correspondence:** Nikolay Botushanov. Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria. E-mail: nbotush@gmail.com
Received: 15-Apr-2025
Revised: 27-Jan-2026
Accepted: 05-Feb-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Total Daily Energy Expenditure (TDEE) is a dynamic parameter influenced by basal metabolic rate (BMR), thermic effect of food (TEF), and activity-related energy expenditure (AEE). With aging, all components of TDEE undergo measurable declines due to changes in body composition, hormonal regulation, and physical activity. Understanding these age-related changes is critical for addressing malnutrition, sarcopenia, frailty, and metabolic diseases in older adults.

AIM: This review synthesizes current knowledge on the physiological, cellular, and behavioral determinants of energy expenditure across the lifespan, with an emphasis on elderly populations.

METHODS: A comprehensive literature analysis was conducted, including randomized controlled trials, observational cohort studies, and mechanistic research, focusing on age-related trends in BMR, TEF, AEE, non-exercise activity thermogenesis (NEAT), and organ-specific metabolic rates.

RESULTS: Aging is associated with reductions in fat-free mass (FFM) and specific metabolic rates of major organs. Mitochondrial dysfunction, decreased Na^+/K^+ ATPase activity, and diminished protein synthesis contribute to lower BMR. TEF declines due to reduced sympathetic responsiveness. AEE and NEAT are significantly impacted by behavioral, neurological, and structural limitations, leading to a progressive fall in total energy expenditure. Notably, higher AEE is independently associated with reduced mortality risk and better physiological resilience in older adults.

CONCLUSION: Age-related energy expenditure decline is multifactorial and partially modifiable. Preservation of physical activity and metabolic health through targeted interventions may mitigate the adverse effects of aging on energy balance and overall health.

Introduction

Feeding is essential for our survival and represents a multisensory experience that integrates gustatory, visual, auditory, and olfactory stimuli, all of which converge on brain centers involved in the regulation of appetite and satiety. Nutrition in older individuals is critical for preserving age-appropriate muscle strength and must be adapted to the physiological changes of aging. The burden of multimorbidity and comorbidities directly impacts both the quality and duration of life.

Recognizing age-related changes in energy expenditure is essential to understanding the mechanisms of appetite regulation. These two processes, energy intake and expenditure, are interdependent facets of the same metabolic coin, and their balance is vital for maintaining body weight and integrity, as well as influencing the onset and course of many diseases. A complex network of interconnected physiological systems orchestrates energy intake and expenditure to regulate body weight and ensure species survival.

Key hormones such as ghrelin stimulate appetite and food intake, while others such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), amylin, and cholecystokinin (CCK) suppress appetite and energy intake. Along with adipokines and pancreatic hormones, these signals are integrated by the central nervous system (CNS) to regulate feeding behavior. Humans eat to meet their total daily energy expenditure (TDEE), the majority of which is composed of resting metabolic rate (RMR), while the most variable and behavior-dependent component is activity-related energy expenditure (AEE). Brown adipose tissue (BAT) also contributes to TDEE, though its long-term effect on energy balance remains uncertain.

The obesogenic environment typical of industrialized countries promotes excessive caloric intake and low physical activity, resulting in weight gain.

However, weight regulation is not simply a matter of "eat less and exercise more" because both appetite and TDEE undergo adaptive changes that facilitate weight regain after loss. Over recent decades, lifestyle changes have led to food intake far exceeding physiological needs. This, combined with our metabolic regulation shaped by millennia of evolution in energy-scarce environments, has resulted in habitual overeating beyond our true energy requirements—arguably the primary driver of the global obesity epidemic. Maintaining energy balance requires equilibrium between caloric intake and expenditure. This balance is fundamental to overall homeostasis. However, how the main components of energy balance, food intake and TDEE, change with age remains incompletely understood.

With aging, energy intake and output decline. Limited literature exists on age-related changes in these mechanisms, primarily due to the logistical and ethical challenges of conducting randomized controlled trials in older and very old adults. Consequently, much of the available data derives from observational population studies, which carry inherent methodological limitations. A deeper understanding of these processes is crucial. It may help determine whether the observed changes represent adaptive responses to an aging body or are linked to the development of pathological conditions that directly affect life expectancy and quality of life. As global life expectancy continues to rise, answering these questions becomes increasingly vital.

Components of the total daily energy expenditure

Total Daily Energy Expenditure (TDEE) is determined by three components:1)Basal Metabolic Rate (BMR); 2) Physical Activity Energy Expenditure (PAEE); 3) Thermic Effect of Food (TEF). (See Figure 1).

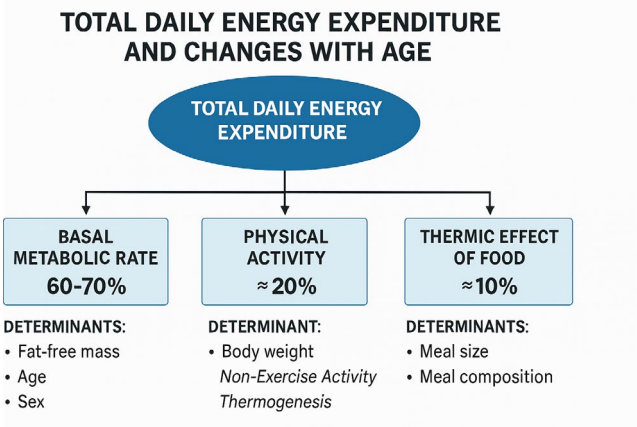

Figure 1: Main components and determinants of total daily energy expenditure

Basal Metabolic Rate

Basal metabolic rate (BMR) represents the energy required to sustain vital physiological processes (e.g., cellular function, respiration, circulation) at complete rest and accounts for approximately 60–70% of TDEE in sedentary individuals. BMR can be divided into sleeping metabolic rate and awake resting metabolic rate, the latter being approximately 10% higher [1]. BMR is ideally measured under strict standardized conditions in a thermoneutral environment [2]. Due to the difficulty in maintaining these conditions, *Resting Energy Expenditure* (REE) is often measured in clinical settings and is about 5% higher than BMR. Although BMR and REE are used interchangeably, REE is more commonly assessed in clinical practice and research. REE is measured by *indirect calorimetry*, an open-circuit method where the patient inhales ambient air and the difference in oxygen (O_2) and carbon dioxide (CO_2) concentrations between inhaled and exhaled air is used to calculate energy expenditure (EE) [3] and substrate oxidation (e.g., fats and carbohydrates).

In clinical settings, REE is measured in the morning after at least an 8-hour fast, and subjects should refrain from moderate to intense physical activity for 24–48 hours beforehand. When these conditions are followed, the coefficient of variation in repeat measurements is approximately 5% [4]. Portable indirect calorimeters exist but typically measure only O_2 consumption and not substrate oxidation, making them less accurate [5], [6]. When determining REE, factors like height, weight, sex, and ethnicity are considered. The most used formulas of *Harris–Benedict* [7] and *Mifflin–St. Jeor* [8] are applicable at the population level but may under- or overestimate REE by more than 10% in 30–40% of adults [9].

REE largely depends on body size and composition, particularly *fat-free mass* (FFM), which includes total body water, proteins, carbohydrates, soft tissues, and bone minerals. FFM accounts for 50–70% of REE variability between individuals. Although often considered synonymous with muscle mass, FFM includes metabolically heterogeneous tissues. For example, the brain, heart, kidneys, and liver, which make up only 5–6% of body weight, account for approximately 60% of REE [10], [11]. In contrast, skeletal muscles, adipose tissue, and bone comprise a larger portion of body mass but contribute only 20–30% of REE. Despite its lower metabolic rate per gram, skeletal muscle is a strong predictor of REE due to its volume [10]. Adipose tissue, although energetically sparse (4 kcal/kg/day), also contributes, especially in obesity [12]. REE declines with age, mainly due to reductions in FFM [13].

Age-related decreases in organ and tissue metabolic rates are also observed, likely due to reductions in cellular mass, decreased Na^+/K^+-ATPase activity, and lower norepinephrine levels, reflecting decreased physical activity, dietary intake, and protein synthesis [14]. In general, men have higher absolute REE than women, but this difference is less

pronounced when adjusted for body fat [15]. In adulthood, growth no longer contributes to BMR, making physical activity and body composition the primary factors influencing energy needs. The diversity of body size, composition, and habitual activity across populations with different geographic, cultural, and economic backgrounds makes it difficult to define universal energy requirements based on average TDEE. To account for variation in physical activity, TDEE is often calculated using factor-based estimations that combine time spent on routine tasks and the energy expenditure associated with those activities.

Thermic Effect of Food

The thermic effect of food (TEF) represents the energy expended for the digestion, absorption, and storage of nutrients. In adults consuming a mixed diet, TEF accounts for approximately 10% of total daily energy expenditure (TDEE) [16]. TEF is proportional to the energy and micronutrient content of food. Protein intake generates a higher TEF compared to fats or carbohydrates [16]. The decline in TEF with age [17], [18] may be attributed to changes in β-adrenergic sensitivity, resulting in reduced postprandial sympathetic stimulation [19]. Data on changes in TEF with weight gain or loss in individuals with or without obesity are inconsistent [20]. Some studies suggest that low TEF may serve as a predictive factor for future weight gain [21].

Activity Energy Expenditure

Activity energy expenditure (AEE) is the most variable component of TDEE and depends on body size and movement. AEE is sometimes expressed as the Physical Activity Level (PAL), which represents the ratio of TDEE to basal metabolic rate (BMR). In the absence of physical limitations, PAL varies significantly among individuals. For example, PAL values around 1.2 are typical for sedentary individuals, while values exceeding 4.0 have been recorded in elite athletes during competition (e.g., Tour de France cyclists, Arctic sled haulers, or Nordic skiers). However, such high levels cannot be sustained long-term [22]. PAL values of 2.8 to 3.0 can be maintained for short periods during intense athletic training but are unlikely to reflect annual averages [22]. In the general population: AEE can be further categorized into exercise thermogenesis and non-exercise activity thermogenesis (NEAT), which includes energy expenditure from occupational tasks, sitting, standing, and other daily activities (see Figure 1).

Measuring AEE in laboratory or everyday settings is challenging. In research, AEE can be assessed via whole-room indirect calorimetry—experimental chambers resembling small hotel rooms where individual components of TDEE can be measured during exercise, rest, and sleep. However, due to the confined space and scheduling limitations, such measurements may not accurately reflect AEE and TDEE under real-life conditions. The doubly labeled water (DLW) method is the most accurate approach for measuring TDEE [23], [24]. This method involves the intake of stable (non-radioactive) isotopes of hydrogen (2H, deuterium) and oxygen (18 O). The labeled 2H is excreted from the body as water (primarily in urine and to a lesser extent through respiration and sweat), while 18O is eliminated both as water and as CO_2 in exhaled air. Thus, the difference in elimination rates reflects CO_2 production over the measurement period (typically 7–14 days), which is used to estimate TDEE [23], [25]. AEE can then be calculated as: *AEE* = *TDEE* – *BMR* and *PAL* can be calculated as**:** TDEE/BMR.

The limitation of this method is that it does not provide information about the type or intensity of physical activity. Therefore, portable activity monitors are more suitable for this purpose. Although most devices demonstrate reasonable accuracy, they estimate AEE as a percentage of TDEE using predictive equations, and significant variability exists among both commercial and research-grade monitors [26]. Activity monitors that incorporate additional biosignals (e.g., heart rate) may improve the accuracy of AEE and TDEE estimations [26].

Changes in Total Daily Energy Expenditure with Age

In attempts to theoretically explain aging, considerable attention has been paid to the role and significance of total daily energy expenditure (TDEE), due to the observed correlation between high TDEE in short-lived mammals and lower TDEE in long-lived species. Some have proposed that TDEE is biologically capped over the lifespan of a given species, and that excessive short-term expenditure may accelerate aging processes [27]. However, other studies strongly criticize and challenge the so-called "rate of living theory" (ROLT) related to TDEE [28], [29]. Energy expenditure is often assumed to be a driver of aging without a full understanding of the age-related changes in the individual components of TDEE.

A deeper understanding of these changes could reveal potential interventions to support healthy longevity. For example, it remains unclear why activity energy expenditure (AEE) declines with age across all mammalian phylogenies. While many aging hypotheses implicate metabolic rate, debate continues around the role of TDEE changes and their potential effects on lifespan extension [30]. With age, TDEE follows an inverted U-shaped trajectory. In the first two decades of life, TDEE approximately doubles, mainly due to increases in body mass. In the following two decades (ages 17 to 40), TDEE plateaus, corresponding with relatively stable body weight during this life stage. After age 40, TDEE begins to decline. By age 75, individuals show TDEE levels like those of

children aged 7–11 years, despite having significantly greater body mass [31]. This pattern is reflected in the current dietary guidelines issued by FAO/WHO/UNU [2]. For example, a person aged 18–29.9 years weighing 70 kg is recommended a daily caloric intake of 2550 kcal/day, whereas a person over the age of 60 with the same body weight is advised to consume 2050 kcal/day. This represents an approximate reduction of 500 kcal/day in TDEE after the age of 40 and highlights the overall decline in energy expenditure that accompanies aging and changes in body composition.

A dynamic balance exists between body mass and the components of total daily energy expenditure (TDEE). The ratio of energy intake to TDEE regulates body weight. An increase in energy intake without a corresponding rise in resting energy expenditure (REE) and activity energy expenditure (AEE) leads to weight gain. Similarly, an increase in TDEE without dietary compensation results in weight loss. Aging is associated with reductions in all components of this equation: body mass, REE, AEE, and the thermic effect of food (TEF). However, it remains unclear which of these is the primary driver of the observed change. One possibility is that a reduction in energy intake alone leads to weight loss. Another hypothesis suggests that a decline in the energy intake-to-(REE + AEE) ratio may compensate for the reduced body mass [32]. The decline in TDEE with age is driven by a combined reduction in both REE and AEE. Potential contributors to this decrease include:

1. Changes in Resting Metabolic Rate with age

Basal metabolic rate (BMR) accounts for 60–80% of total daily energy expenditure (TDEE). As previously noted, of all TDEE components, resting energy expenditure (REE) is the most frequently measured due to the accessibility and affordability of the equipment required, and the relatively short time required for assessment in humans (around 30–60 minutes). REE measurement is typically combined with assessments of body fat percentage and fat-free mass (FFM). Since FFM accounts for more than 60% of daily REE, its quantity is used to adjust the obtained REE values. This adjustment helps account for many individual differences in REE, though it is important to note that REE is not constant among older adults. For example, higher body mass in young adults, when adjusted for FFM, is associated with lower REE [33].

Animal studies suggest that weight gain is associated with an increase in tissues with low energy demands (fat) without a proportional increase in highly metabolically active tissues (e.g., brain, liver, kidneys) [34]. Thus, when body weight increases but skeletal muscle mass (which has lower metabolic activity) increases disproportionately compared to other FFM components, total REE decreases because the mass of highly active tissues remains unchanged [33]. In aging, body mass typically decreases. Aging is associated with a progressive decline in whole-body REE at a rate of 1–2% per decade after age 20.[35] This decrease is closely linked to the reduction in FFM, which consists of metabolically active tissues and organs [36]. However, there is ongoing debate as to whether the decrease in REE is entirely due to changes in FFM, as some evidence suggests that body composition adjustments do not fully account for the REE differences between young and older adults [37].

In other words, REE remains significantly lower in older adults even after correcting for differences in body composition. A more accurate estimate of REE can be calculated using the equation: $REE=\sum(M_i \times Met_i)$. Where M_i represents the mass of a given organ, and Met_i is the specific metabolic rate of that organ, expressed in kcal/kg/day, reflecting the metabolic rate of the cells within that organ. Age-related changes in organ mass (M_i) were first evaluated in 1926 based on autopsy studies involving approximately 2200 men and women [38]. These studies found that from age 20 to 80, there is a 32% reduction in liver mass, a 23% reduction in kidney mass, a 55% reduction in spleen mass, and a 10% increase in heart mass. While this and other studies demonstrate age-related reductions in most organ masses [38], [39], [40], they have been criticized for lacking information about cause of death and for potential fluid shifts that may have occurred between time of death and organ measurement. However, in vivo data support these findings. He Q et al. analyzed whole-body magnetic resonance imaging results and confirmed that most organs decline in mass with age [41]. The estimated percentage change in organ mass from age 20 to 80 was calculated using equations. The results showed that the mass of the brain, bones, kidneys, liver, and muscles decreases at relatively similar rates—between 10–20%—over that period, while the spleen exhibited a dramatic 38% loss of tissue mass [41]. These findings indicate that the reduction in organ mass with age clearly contributes to the age-related decline in REE (Figure 2).

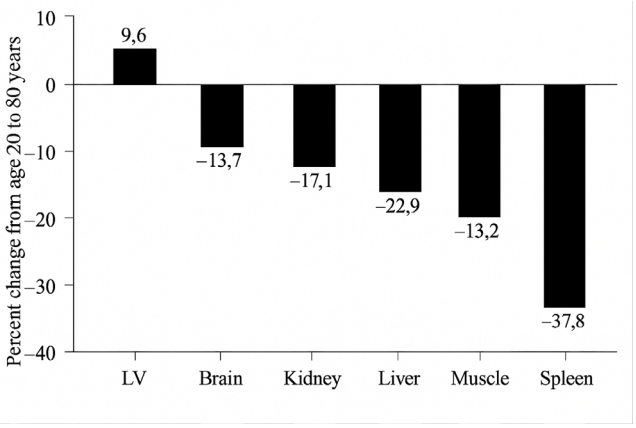

Figure 2: Percent change in organ mass between ages 20 and 80 [41]. Adapted from He Q, Heshka S, et al. Smaller Organ Mass with Greater Age, Except for Heart. J Appl Physiol. 2009

The other component of the equation for calculating resting metabolic rate (RMR), the specific metabolic rate (Meti), depends on factors such as the

cellular fraction within a given tissue, mitochondrial proton leak, protein turnover rate, and Na^+/K^+-ATPase activity [42]. As a result, Meti cannot be easily determined in vivo. Most of the existing literature relies on approximations based solely on organ mass or total body fat-free mass (FFM), under the assumption that specific metabolic rates remain constant across the lifespan. Until recently, this assumption went largely unchallenged. Wang Z et al. conducted a comprehensive study of organ mass and estimated specific metabolic rate across adults aged 23 to 88 [43]. Organ volumes were measured using whole-body magnetic resonance imaging (MRI), excluding low-energy tissues like adipose tissue. The cellular fraction of organs was also assessed, based on the premise that aging increases extracellular components, which do not contribute to heat production.

The precision of this method depends on accurate estimation of body cell mass and extracellular water. Researchers used total body potassium to estimate cellular mass, deuterium dilution for total body water, and a combination of both to determine extracellular water. Their findings showed that the model predicted RMR accurately up to age 50 but significantly underestimated it beyond that. This underestimation likely reflects a lower cellular fraction in FFM in older adults, which reduces metabolic rate per unit of tissue. Therefore, assuming homogeneous metabolic activity across age groups may lead to inaccuracies when estimating age-related declines in RMR.

a) The Protective Role of Physical Activity on Age-Related RMR Decline

Physical activity plays a key role in slowing the age-related decline in RMR due to its significant influence on maintaining body composition in highly active older adults [44]. Aerobic capacity and total exercise volume are positively correlated with RMR, suggesting that activity level contributes to resting energy expenditure. Numerous studies indicate sex-specific effects of chronic physical activity on RMR [45], [46]. In older physically active women—particularly those who had trained in endurance running for approximately 18 years—RMR adjusted for FFM did not decline. Similarly, prior engagement in athletics or swimming was associated with preserved FFM-adjusted RMR in elderly women [45]. These data suggest that endurance exercise helps maintain RMR. Interestingly, older active women also maintained FFM comparable to younger women. In contrast, among highly active older men, RMR adjusted for FFM was lower than in younger counterparts. Subgroup analysis showed that both exercise volume and energy intake were positively correlated with FFM-adjusted RMR. When younger and older groups were matched for either weekly training hours or energy intake, the difference in RMR disappeared. This suggests that RMR in men declines with age despite regular endurance exercise, but the reduction is closely tied to decreased exercise volume and energy intake. Men who are able to sustain high levels of physical activity and caloric intake as they age may be able to preserve their RMR.

b) Energy Balance, Physical Training, and RMR: Insights from Experimental Studies

Bullough RC et al. investigated the potential mechanisms underlying increased resting metabolic rate (RMR) in physically trained individuals [47]. Using a set of controlled experiments, the researchers evaluated the effects of four energy balance states: high energy balance (high intake + exercise), low energy balance (low intake + no exercise), negative energy balance (low intake + exercise), and positive energy balance (high intake + no exercise) in both trained and untrained individuals. They found that RMR was higher in trained individuals only under conditions of high energy balance, in which caloric intake matched the energy expended through physical activity. This increase in RMR was partially attributed to elevated norepinephrine levels. Notably, a reduction in norepinephrine levels was observed in all trained individuals who transitioned from high to low energy balance. Correlation analysis revealed that norepinephrine was strongly associated with the change in RMR during this transition. In contrast, levels of triiodothyronine (T3), glucose, insulin, and epinephrine remained unchanged, suggesting they do not significantly affect RMR in this context. These findings suggest that overall energy intake contributes to RMR even in states of energy balance, and that age-related reductions in RMR may be partly due to attenuated norepinephrine release during chronic physical training in older adults.

c) The Impact of Disease States on RMR in Aging

Aging is accompanied by various diseases that may increase or decrease RMR. Conditions such as Alzheimer's disease, chronic obstructive pulmonary disease (COPD), congestive heart failure, Parkinson's disease, diabetes mellitus, malnutrition, and cancer are all associated with altered RMR [48]. Diseases that typically elevate RMR include COPD [49], lung cancer [50], and diabetes [51]. Conversely, RMR tends to decline in conditions linked with negative energy balance and weight loss, such as Alzheimer's disease [52], renal failure [53], and malnutrition [54]. Although hypermetabolism has been proposed as a driver of clinical deterioration in chronic diseases, most studies conclude that reduced energy intake is the main mediator of negative energy balance and weight loss in such conditions [55]. It is important to note that many studies have not adjusted RMR measurements for fat-free mass (FFM), which may confound interpretations. Moreover, it remains unclear whether changes in cellular composition or shifts in specific organ

metabolic rates contribute to the observed alterations in RMR in aging and chronic illness.

d) Tissue-Specific Metabolic Rates and Their Role in Age-Related Decline in RMR

As previously noted, tissue-specific metabolic rates are determined by processes such as mitochondrial proton leak, protein metabolism, and Na^+/K^+ ATPase activity at both the cellular and tissue levels. Changes in these processes support the notion that tissue-specific metabolic rates contribute to the age-associated decline in resting metabolic rate (RMR). When cellular ATP demand is low, mitochondrial proton leak may account for approximately 16–21% of RMR [56]. Paradoxically, aging is associated with increased proton leak, which would theoretically elevate RMR [57]. However, this process may also explain the observed decrease in specific metabolic rate per unit of tissue, as the energy lost through proton leak is not utilized for useful biological work. Na^+/K^+ ATPase is a critical enzyme found in all cells, responsible for maintaining the sodium and potassium gradient across the plasma membrane. Its activity is linked to interspecies differences in RMR, correlating with variations in body size across mammals and reptiles [58], [59]. Multiple animal studies have demonstrated age-related declines in Na^+/K^+ ATPase activity in cardiac [60] and brain tissues [61]. Similar changes have been reported in human erythrocytes [62] and lymphocytes [63]. Although some studies offer conflicting findings [64], the predominant body of evidence suggests that reduced Na^+/K^+ ATPase activity contributes to the decrease in RMR observed with aging.

e) Protein Turnover and Age-Related Changes in Metabolic Rate

Maintaining protein balance through energy-dependent processes governing amino acid synthesis and degradation is a key determinant of resting metabolic rate (RMR) [56]. Overall, aging in both humans and animals leads to a reduction in whole-body and tissue-specific protein turnover [65], [66], [67]. However, some studies report no significant effect of altered protein turnover on RMR after adjusting for fat-free mass (FFM) [68]. Most investigations rely on tissue models, particularly skeletal muscle, due to its relevance in sarcopenia. It is widely accepted that muscle protein breakdown rates remain stable with age, while protein synthesis—both in the fasting and postprandial states—declines with aging [69]. Older adults show a blunted increase in muscle protein synthesis following the ingestion of essential amino acids [70]. The mechanisms behind reduced protein synthesis are not fully elucidated but may involve decreased levels of anabolic hormones and impaired nutrient uptake. Testosterone levels correlate with myosin heavy chain synthesis, and testosterone replacement in hypogonadal men has been shown to restore muscle protein synthesis [71], [72]. In contrast, long-term growth hormone administration in older adults does not significantly affect muscle protein synthesis [73]. Altered nutrient uptake in skeletal muscle may also contribute to age-related declines in protein synthesis. In older individuals without overt type 2 diabetes, insulin resistance at the muscle level impairs protein synthesis, potentially due to defects in endothelial-dependent vasodilation [74]. Supporting this, aerobic exercise—which enhances vasodilation—reduces insulin resistance and improves muscle protein synthesis in the elderly [75]. In summary, the observed age-related decline in tissue-specific metabolic rates appears to be associated with decreased Na^+/K^+ ATPase activity and reduced protein synthesis.

2. Age-Related Changes in Physical Activity Energy Expenditure

With aging, physical activity levels and mobility decline across species—including humans, non-human primates, dogs, rodents, and insects [76]. Physical activity energy expenditure (AEE) includes two categories: energy expended during structured exercise and that expended during routine daily activities (see Figure 1). AEE is highly variable [77] and remains the most difficult component of total daily energy expenditure (TDEE) to measure, and therefore the least studied in the context of aging. AEE ranges broadly in humans—from 262 kcal/day in older adults with dementia [78] to 1434 kcal/day in Mount Everest climbers [79]. Like other TDEE components, AEE is influenced by body mass, though the effect is weaker compared to resting metabolic rate (RMR). While fat-free mass (FFM) accounts for over 60% of RMR, it only explains ~10% of AEE [80]. Thus, AEE is largely independent of FFM, and its age-related decline primarily reflects reductions in movement frequency and intensity (e.g., walking, household chores, standing, and sedentary behavior). Studies in families and monozygotic twins suggest that AEE has a genetic basis [81]. Stronger evidence comes from animal studies, where a 72% reduction in spontaneous physical activity was observed before significant weight gain in obesity-prone mice [82]. Moreover, mutations in the foraging gene are associated with reduced motor behavior in adult Drosophila [83] Joosen et al. [84] evaluated physical activity levels and AEE using respiratory chambers and free-living assessments in monozygotic and dizygotic twins. They found that genetics accounted for 72% of AEE variation and 78% of variability in physical activity levels. These associations were attenuated but remained significant after adjusting for anthropometric traits (e.g., body fat mass). Conversely, a similar study in children reported weaker genetic influence on AEE, which disappeared after adjusting for anthropometric and demographic factors [85]. Although physical activity originates from higher-order brain centers, these results suggest that

the decision to be active is modulated by genetic predisposition. Despite the genetic component, AEE consistently declines with age. Using doubly labeled water and indirect calorimetry, Johannsen et al. [86] measured TDEE and RMR and calculated AEE with the formula: *AEE = TDEE − [RMR + (0.1 × TDEE)]*. They studied 206 men and women across three age groups: 20–34, 60–74, and ≥90 years. Interestingly, only the ≥90 group showed a significant reduction in AEE when adjusted for body mass [86]. A separate longitudinal study [87] followed 316 individuals for 25 years, showing AEE reductions of 9% and 25% in the 60–74 and >75-year groups, respectively. This decline was the primary determinant of age-related reductions in TDEE. Importantly, reductions in FFM—a normal biological adaptation to aging—did not fully explain the observed decrease in AEE. A number of epidemiological studies have shown that physical activity declines with advancing age. However, most of these studies rely on self-reported data, which introduces significant discrepancies compared to actual physical activity levels [88], [89], [90], [91]. Accurately quantifying activity energy expenditure (AEE) is challenging, which is why there is limited literature on AEE in older adults. Troiano et al. [92] conducted a large-scale study in which accelerometers were placed on the thighs of 4,867 individuals across different age groups. The device functioned as a small (2.0 × 1.6 × 0.6 inch), lightweight (42.5 g) accelerometer capable of measuring accelerations ranging from 0.05 to 2 G and frequencies from 0.25 to 2.5 Hz—corresponding to most types of human motion. An analog-to-digital converter collected data at a frequency of 10 Hz, with the values aggregated into one-minute epochs. A key feature of these accelerometers was their ability to count the number of accelerations, where a higher count over a given period indicated higher intensity activity. Thresholds for these counts were established and used to classify activity intensity as moderate or vigorous.

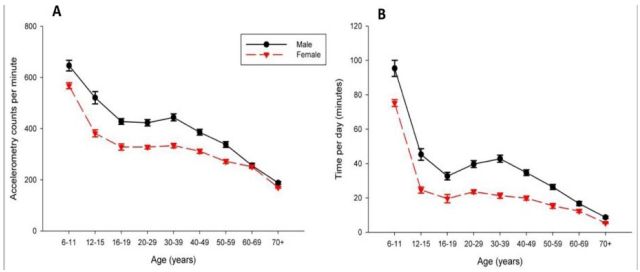

Figure 3. Age-related decline in physical activity across the lifespan. Panel A: Accelerometry counts per minute, a proxy for physical activity intensity, decrease progressively with age in both sexes. Panel B: The duration of daily moderate-to-vigorous physical activity also declines significantly, especially after early adulthood. Data derived from NHANES accelerometer study (Troiano et al., 2008) including 4,867 individuals aged 6 to 70+ years.[92]

The data showed that moderate-to-vigorous physical activity declined sharply after age 11, with another noticeable drop after age 39. Both men and women exhibited a ~55% decrease in accelerometer-recorded counts of moderate-to-vigorous activity between the ages of 39 and 70+. In terms of time spent in moderate or vigorous activity, men's daily activity decreased from 42 minutes per day (21 min/day in women) to just 8.7 minutes per day (5.4 min/day in women) between the ages of 39 and 70+. This represents an approximate 75% reduction in time spent in moderate-to-vigorous physical activity for both sexes. These findings underscore the substantial decline in AEE with increasing age (Figure 3).

3. Non-Exercise Activity Thermogenesis changes with age

In addition to voluntary physical activity, AEE includes involuntary movements known as non-exercise activity thermogenesis (NEAT) (see Fig. 1). In its strictest definition, NEAT encompasses unconscious, spontaneous, and non-volitional movements only [93]. While volitional AEE is a major component of TDEE, under normal conditions it has a smaller determining effect on total expenditure compared to NEAT [94]. NEAT is even more challenging to quantify, as standard equipment such as hip-mounted accelerometers fails to capture many movements contributing to it (e.g., seated or standing postural adjustments). To address these challenges, Harris AM et al. conducted a case–control study comparing healthy older adults (>70 years) with younger adults (30–40 years) in terms of fat-free mass (FFM) and physical activity levels.[95] The researchers measured NEAT using specially designed triaxial accelerometers and inclinometers, which detect acceleration relative to gravitational force. These devices assessed posture allocation, tracking time spent lying, sitting, standing, and moving over a 10-day period. The results showed that older adults walked 3 miles less per day, spent 131 minutes more per day sitting, and 110 minutes less standing than their younger counterparts [95]. These findings suggest that NEAT—as reflected by time spent in seated, standing, and ambulating postures—is markedly reduced even in older individuals with FFM levels comparable to those of young adults.

4. Age-Related Changes in the Biological Regulation of Activity-Related Energy Expenditure

Aging increases the tendency toward physical inactivity. However, it remains unclear whether biological changes associated with aging drive a person's desire to be less active—and whether this tendency is inherently part of aging and shaped by evolution. The answer is not yet definitive. In humans, it likely involves a complex interplay of biological, psychological, and social factors [96]. Nevertheless, the potential role of biological factors should not be overlooked. AEE is closely linked to body weight regulation. Prolonged caloric restriction reduces

physical activity levels [97], while overfeeding increases activity in lean individuals [98]. A study by Martin et al. supports the connection between body mass and activity: using the doubly labeled water method, they found that AEE was significantly reduced in overweight adults following a 25% reduction in caloric intake over three months [97]. These findings align with anecdotal reports of apathy and decreased movement in individuals undergoing semi-starvation, suggesting that reduced physical activity serves as a survival mechanism for conserving energy [99]. Interestingly, in non-human primates, caloric restriction may increase physical activity, possibly due to behavioral changes related to intensified food-seeking [100]. However, such behavior is unlikely to affect AEE in humans given the readily available food in modern environments. Thus, caloric restriction suppresses AEE and may be a protective mechanism against excessive loss of body weight [97]. Given the close association between body weight and AEE, it is plausible that the age-related reduction in AEE serves as a compensatory strategy to mitigate losses in both total body mass [101] and fat-free mass (FFM) [102]. In other words, declining AEE with age may help conserve energy and protect against tissue wasting. It is tempting to interpret this link as a possible explanation for the reduction in physical activity observed with aging.

5. The Relationship Between Longevity and Energy Expenditure

The role of total daily energy expenditure (TDEE) as a key predictor of lifespan is actively debated. A substantial body of literature supports both sides of the argument regarding the importance of energy expenditure in the aging process. This discussion is centered on the so-called “Rate of Living Theory” (ROLT) [103]. Rubner was the first to document a relationship between metabolic rate and body size in animals [104]. He noted that TDEE, when expressed as a function of body size and lifespan, appears relatively fixed. From this, he hypothesized that energy expended more rapidly leads to a shorter lifespan. Further support came from Loeb and Northrop, who demonstrated that cold-blooded animals exposed to elevated ambient temperatures experienced shortened lifespans [105]. Pearl later expanded on these ideas in two key publications, forming the foundation of ROLT [106]. He stated, “Life expectancy is determined by two variables: the constitution of the individual (genetically determined), and the average metabolic rate or energy expenditure.” ROLT has been supported by studies in mammals exposed to manipulated environmental temperatures [107]. However, birds and bats live several times longer than similarly sized mammals with comparable resting metabolic rates (RMR0) [108]. Moreover, rats chronically exposed to cold environments increase their TDEE but do not experience shortened lifespans [109]. Despite criticism, ROLT provides a conceptual framework for exploring how energy metabolism may contribute to aging through cumulative damage caused by byproducts of oxidative metabolism [110], [111]. The theory remains controversial due to several methodological challenges, including the need to adjust for body size, the lack of standardized lifespan definitions, appropriate interspecies comparison methods, and the selection of the most relevant TDEE component—RMR or activity energy expenditure (AEE). Unlike RMR, which shows low variability within species after adjustment for fat-free mass (FFM), TDEE is highly variable both within and across species, even after correcting for body mass [112]. Thus, TDEE may be a more appropriate metric than RMR when testing the validity of ROLT. Speakman presented comprehensive data on energy expenditure (EE), calculated using the doubly labeled water method in mammals and birds, and examined its relationship with lifespan [113]. Among small mammals (<4 kg), EE was inversely proportional to lifespan—even after adjusting for body mass and environmental temperature influences—supporting the Rate of Living Theory (ROLT), as higher EE rates correlated with shorter lifespan. However, human data provides a contrasting perspective. In a study by Manini et al. [30], total daily energy expenditure (TDEE) and resting metabolic rate (RMR) were measured in 302 older adults (70+ years) using doubly labeled water and indirect calorimetry, respectively. The activity-related energy expenditure (AEE) was calculated using the equation*:(TDEE* × *0.90) – RMR.* Participants were followed over eight years to assess mortality risk. Neither resting EE nor tissue-specific EE predicted mortality. However, once AEE was isolated, individuals in the lowest AEE quartile had nearly three times the mortality risk compared to those in the highest quartile. Expressed per standard deviation, a 287 kcal/day increase in AEE was associated with a 32% reduction in mortality risk. Adjustments for sex, health status, and body composition did not alter this association. Comorbidity profiles were similar across AEE quartiles, minimizing potential bias from preexisting illness. While such studies cannot assess lifelong AEE, these findings support the broader conclusion that higher AEE is linked to reduced mortality and better preserved health [114]. This suggests AEE may serve as a strong predictor of longevity.

6. Energy Balance and Its Impact on Long-Term EE

Maintaining energy balance across the lifespan is crucial for physiological function. Energy balance—achieved when energy intake equals expenditure—ensures homeostasis. Deviations result in shifts in body energy stores, primarily through changes in the mass of certain tissues, [115]. which in turn affect EE. With positive energy balance, RMR increases due to the

growth of fat-free mass (FFM); conversely, RMR decreases with weight loss during negative energy balance. If energy intake remains constant after a body mass change, EE will eventually realign with intake, stabilizing weight at a new equilibrium. However, persistent deviations can result in disproportional shifts in EE unrelated to metabolic mass. Several studies [116], [117], [118] have shown that post-weight loss, 24-hour EE may drop by as much as 15% more than predicted based on changes in body composition—a phenomenon known as *metabolic adaptationor a daptive thermogenesis.* Conversely, overfeeding results in higher-than-expected EE [119]. In severely obese individuals, one study noted a persistent decline in RMR following an intense diet and exercise program, with reductions of 275–499 kcal/day observed even six years post-intervention, despite substantial recovery of both FFM and fat mass [120]. This suggests disproportionate changes in EE not only during but long after dynamic weight changes. Beyond changes in body composition, altered efficiency of movement and physical activity with different body weights also affects 24-hour EE. Variations in food intake impact the thermic effect of food (TEF), contributing to overall EE fluctuations. Moreover, RMR does not scale linearly with metabolic mass [121], [122] potentially due to changes in FFM composition. As noted earlier, both weight loss and aging are associated with relatively larger reductions in high-metabolic-rate organs (e.g., liver, heart, kidneys) compared to overall FFM loss. [123].

Conclusion

Age-related changes in total daily energy expenditure (TDEE) are multifactorial and involve progressive reductions in basal metabolic rate (BMR), thermic effect of food (TEF), and activity energy expenditure (AEE). These changes are primarily driven by: Alterations in body composition, notably the loss of fat-free mass (FFM) and disproportionate atrophy of metabolically active organs such as the liver, kidneys, and heart. Declines in tissue-specific metabolic rates, due to reduced Na^+/K^+ ATPase activity, increased mitochondrial proton leak, and impaired protein turnover. Decreased physical activity, both volitional and non-volitional (NEAT), resulting from sarcopenia, reduced mobility, and behavioral adaptations, including lower motivation or opportunity for physical engagement.Metabolic adaptation, which may persist long after weight loss or in the context of chronic illness, further lowering resting energy demands. Importantly, AEE emerges as a strong, independent predictor of longevity. Higher AEE is consistently associated with reduced mortality and better preservation of physiological function in older adults. Physical activity not only mitigates the decline in resting metabolic rate but also supports muscle mass retention and metabolic resilience.Understanding these dynamics is crucial for developing personalized strategies to maintain energy balance, prevent frailty, and delay the onset of age-associated chronic diseases. Interventions promoting sustained physical activity, nutritional adequacy, and metabolic health across the lifespan are essential pillars of healthy aging.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Feb 28; 14(1):33-37.
https://doi.org/10.3889/oamjms.2026.12042
eISSN: 1857-9655
Category: *B – Clinical Sciences*
Section: *Infective Diseases*

Clinical Outcomes of Home Parenteral Antibiotic Therapy Using Accufuser®

Amjad S. Al Seraya, Kholoud Abdulaziz Bin Haikel*,

King Abdulaziz Medical City, King Abdullah International Medical Research Center, National Guard Health Affairs, Riyadh, Saudi Arabia

Citation: Al Seraya AS, Bin Haikel KA. Clinical Outcomes of Home Parenteral Antibiotic Therapy Using Accufuser®. Open Access Maced J Med Sci. 2026 Feb 28; 14(1):33-37. https://doi.org/10.3889/oamjms.2026.12042
Keywords: Accufuser®; infection; antibiotic
***Correspondence:** Kholoud Abdulaziz Bin Haikel. King Abdulaziz Medical City, King Abdullah International Medical Research Center, National Guard Health Affairs, Riyadh, Saudi Arabia. E-mail: dr-kholoud1@hotmail.com
Received: 05-Mar-2025
Revised: 11-Feb-2026
Accepted: 20-Feb-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: In September 2020, the home health care program introduced the elastomeric pump Accufuser® to the home parenteral antimicrobial therapy program as a new means of administering medications. We aim to assess the clinical outcomes of this recent addition in comparison to traditional administration methods.

METHODS: This is a retrospective cohort study conducted at the Adult Home Health Care Services in King Abdulaziz Medical City, Riyadh. We enrolled all the patients who were accepted at the home parenteral antimicrobial program from January 1, 2019 to May 31, 2022. The outcomes of the group of patients who received therapy through Accufuser® and the group that used other administration methods were compared.

RESULTS: We included 285 patients in this study, among whom 167 (58.6%) were females. Eighty-nine (31.2%) patients utilized Accufuser®, while the rest used direct intravenous (IV) (71, 24.9%) and IV piggyback (125, 43.9%). A significant reduction in the duration of visits (P=<0.00) and the number of daily visits (P=<0.00) was observed in the group that used Accufuser®. Both groups had similar rates of therapy completion (P=0.14). No significant difference was noticed in the rates of complications (P=0.57) or the rates of mortality between the two groups (P=0.14).

CONCLUSION: The Accufuser® device is a safe administration method that reduces both the duration and the number of daily visits.

Introduction

Outpatient and home parenteral antibiotic therapy (OHPAT) programs are accepted modes of providing healthcare with low cost, high efficacy, and high safety [1]. The home parenteral antimicrobial program was adopted in 2004 as part of the Home Health Care (HHC) Department program in King Abdulaziz Medical City (KAMC). The program started with the treatment of patients with diabetic foot who used to require three months of inpatient treatment with intravenous (IV) antibiotics. The program expanded slowly but remained restricted to therapy with once-per-day medications. Later, the program was augmented to cover the treatment of all types of infections and accommodate medications with frequent dosages. The program used a visiting nurse model, wherein a nurse visits the patient's residence and administers the prescribed IV medications at the appropriate time. For most patients, a peripherally inserted central catheter (PICC) was utilized, and the medications were administered through an infusion bag or direct IV. In 2011, a study by Baharoon et al., which aimed to evaluate the program and its outcomes, reported that the program was both clinically and economically effective [2]. Out of the 155 enrolled patients, 86% completed the program successfully, and only 8.5% had to be readmitted [2]. However, despite its success, the travel time, duration of visits, and frequent daily doses remained tremendous challenges to this model of care.

Since its commencement, the program at KAMC has aimed to expand and adopt new technologies to provide better care, serve more patients, and save resources. In September 2020, the program started utilizing elastomeric infusion devices. The elastomeric pump Accufuser®, a product of Woo Young Medical Co., Seoul, South Korea, was selected to be utilized in the program. This product received Food and Drug Administration (FDA) approval in 2002 and has been in the market since [3]. Given its extensive presence in the market, several studies have been conducted to assess its quality and reliability in

OHPAT programs. These studies assessed the stability of a variety of commonly used antimicrobial agents and concluded that Accufuser® could be safely used to administer a continuous infusion of those agents for up to 48 hours [4], [5], [6], [7], [8], [9], [10]. A study evaluating nurses' experience with Accufuser® reported that 299 nurses (100%) found the pump easy to use, and 270 (100%) found it clinically acceptable [11].

The adoption of new technologies is a means to optimize the care provided to patients and save hospital resources simultaneously. We conducted this study to assess the clinical outcomes of Accufuser®, a newly introduced device, in home parenteral therapy program and its impact on patient care.

Methods

This is a retrospective cohort study conducted at the Adult HHC Service in KAMC in Riyadh. The Adult HHC Service serves more than 800 patients throughout Riyadh City. We evaluated a total of 285 patients who were accepted to the home parenteral antimicrobial program from January 1, 2019 to May 31, 2022. We included all accepted patients who received a minimum of one home visit. All the data were retrieved from the patients' electronic medical records. The study was approved by the institutional review board of King Abdullah International Medical Research Center (RYD-21-419812-113262).

The HHC Department follows strict guidelines in accepting patients into the home parenteral antimicrobial therapy program and utilizing Accufuser® in patient care. Consultations with an infectious disease specialist and a clinical pharmacist must be undertaken prior to referring patients to the HHC. Referral must be done at least 48 hours before the patient's discharge to arrange for venous access and ensure the safety of the administered drugs, as well as to counsel patients and relatives about the program. A PICC was used as a standard measure in most patients. Patient education must be provided during the hospitalization period, which involves instructions on storing the medications and administering them via the infusion pump. During transportation, the medications must be kept in a cooler. A double-checking checklist must be signed by two staff nurses independently.

In September 2020, the elastomeric pump Accufuser® was introduced in the program. Since its introduction, it has been used to administer medications for most patients. In some patients, other administration methods were still utilized even after the adoption of the elastomeric pump due to times of low supply (during the COVID-19 pandemic), the resistance of some patients and caregivers, and preference at times when the medications require a single visit with a short infusion time.

All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented as mean and standard deviation (mean ± SD), while percentages and frequencies were used to describe the categorical variables. The statistical analysis included the use of the Chi-square test to measure the association between the two groups (the group that used Accufuser® and the group that used other methods), as well as the completion of therapy, complications, deaths, and daily visits. The Wilcoxon two-sample test was used to compare the duration of visits between the groups. P-values less than 0.05 were considered statistically significant.

Results

Demographics

We studied a total of 285 patients who were referred to the home parenteral antimicrobial program from January 1, 2019 to May 31, 2022. Females accounted for 167 (58.6%) of our sample. Half of our patients were older than 75 years. Over 70% were comorbid with diabetes mellitus (DM). Up to 98 (34.4%) patients suffered from chronic kidney disease (CKD), and 75 (26.3%) had cognitive impairment.

Table 1: Clinical characteristics of all patients in this study

	n (%)
Female	167 (58.6%)
Male	118 (41.4%)
Age	
< 50	30 (10.5%)
50-64	42 (14.7%)
65-74	70 (24.6%)
>=75	143 (50.2%)
DM	205 (72.0%)
CKD	98 (34.4%)
Cognitive Impairment	75 (26.3%)
Deaths	15 (5.3%)
Total	285 (100%)

Outcomes of Therapy

We assessed the safety and benefits of the newly introduced device by comparing the outcomes of the group of patients that used Accufuser® and the group that received medications through other traditional administration methods. A total of 89 (31.2%) patients received their medications through Accufuser®, 71 (24.9%) through direct IV, and 125 (43.9%) through an IV drip.

Table 2: Outcomes of therapy in the group that used Accufuser® and the group that used other administration methods

	IV push / IV piggyback	Accufuser®	P-value
Total number of patients	196 (68.8%)	89 (31.2%)	-
Completion of therapy	177 (90.3%)	75 (84.3%)	0.14
Complications	41 (20.9%)	16 (18.0%)	0.57
Deaths	12 (6.1%)	3 (3.4%)	0.41
Daily visits (> 1 visit/day)	30 (15.3%)	0 (0.0%)	<0.00*
Duration of visits (mean ± SD)	31.4±13.2	17.3±6.13	<0.00**

* Chi-Square test was used to test the association between the groups with the Daily visits.
** Wilcoxon Two-Sample Test was used to compare the duration of visits between the groups.

Table 2 summarizes the outcomes based on the methods of therapy administration. More than 80% of the patients completed their therapy successfully. No significant difference (P>0.05) was found in the rate of completion of therapy between the patients who used Accufuser® and those who used other methods. Complications were noticed in 16 (18%) patients who used Accufuser® and 41 (20.9%) in those who used other methods of administration, with no significant difference between the two groups (P>0.05). The mortality rate was 12 (6.1%) in the group with the traditional administration methods and three (3.4%) in the group that used Accufuser®, with no significant difference (P>0.05). Not all deaths were related to the infection and its treatment, as some of these were attributed to other conditions. Only the deaths related to infection and/or its treatment were counted as complications of therapy.

Usage of other methods was significantly associated with more daily visits than the use of Accufuser® (P≤0.05). None of the patients in the group that used Accufuser® needed more than one visit daily; however, the group that used other administration methods needed additional daily visits depending on the frequency of the doses of the prescribed medication. Figure 1 presents a visualization of the difference in the duration of visits based on the administration methods used. We did not combine the group of patients that used direct IV and the group that used IV drip because the first method usually takes a shorter time. However, even in this case, Accufuser® was significantly associated with the lowest duration of visit.

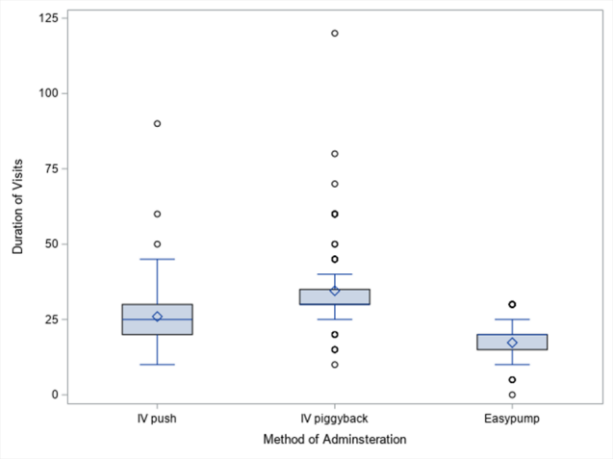

Figure 1: Comparison between durations of visits (in minutes) based on the utilized administration method

Complications of Therapy

In the group of patients that utilized Accufuser®, 18 complications of therapy were observed in 16 (18.0%) patients. As seen in Table 3, The most common complications were related to PICC use, which was seen in seven (7.9%) patients, including two who pulled their own PICCs. Persistent or worsened symptoms were noted in six (6.7%) patients who had to be readmitted and continued on therapy in the hospital. Sepsis complicated the course of therapy in three (3.4%) patients. Three deaths (3.4%) occurred in the patients who used Accufuser; however, only two of those were related to the current infection; the other case was attributed to another condition. As mentioned above, the mortality rate was not significantly higher than the rate noted in patients who did not use Accufuser® (P=0.41).

Table 3: Complications seen in the group that used Accufuser®

Complication	n (%)
PICC-Related	7 (7.9%)
PICC blockage	3 (3.4%)
Pulled PICC	2 (2.2%)
PICC dislodged	1 (1.1%)
PICC site DVT	1 (1.1%)
Persistent or worsening Symptoms	6 (6.7%)
Sepsis	3 (3.4%)
Death	2 (2.2%)
Total	18 (100.0%)

Furthermore, we investigated whether any factor increases or decreases the risk of complications in patients receiving therapy with Accufuser®. As seen in Table 4, gender, being older than 75, DM, CKD, cognitive impairment, and taking drugs that require more than one daily dose were not related to any significant increases in complications of therapy.

Table 4: Factors associated with complications in the group of patients that used Accufuser®

	Complications	No complications	P-value
Gender	16	73	0.53
Male	5 (31.2%)	29 (39.7%)	
Female	11(68.8%)	44 (60.3%)	
Age ≥75 years old	6 (37.5%)	37 (50.7%)	0.34
DM	13 (81.3%)	50 (68.5%)	0.38
CKD	5 (31.3%)	22 (30.1%)	1.00
Dementia	3 (18.8%)	20 (27.4%)	0.75
Frequency (>1/day)	7 (43.8%)	37 (50.7%)	0.62

Statistics of Accufuser® Use

Table 5 presents the diagnoses of the patients who received treatment through Accufuser®. Up to 89 patients were referred with 92 diagnoses. Urinary tract infection (UTI) was the most common diagnosis (32, 34.8%), followed by bacteremia (19, 20.7%) and osteomyelitis (17, 18.5%). Almost half of the cases of bacteremia originated from a UTI (8, 47.7%).

Table 5: Diagnoses of patients who used Accufuser®

Diagnoses	n (%)
UTI	32 (34.8%)
Bacteremia and sepsis	19 (20.7%)
Urosepsis	8 (47.7%)
Osteomyelitis	17 (18.5%)
Septic arthritis	8 (8.7%)
Infective endocarditis	5 (5.4%)
Intracranial infection	4 (4.3%)
Soft tissue infection	2 (2.2%)
Liver abscess	2 (2.2%)
Pneumonia	2 (2.2%)
CMV Retinitis	1 (1.1%)
Total	92 (100%)

A total of 82 pathogens were isolated, as seen in Table 6. *Escherichia coli* was the most commonly isolated pathogen (30, 36.6%), followed by *Streptococci* (18, 22.0%) and *Klebsiella pneumoniae* (10, 12.2%). Candida was the only isolated fungus, and it was seen in four patients (4.9%). Varicella-zoster

virus, the only isolated virus, was isolated from one patient (1.2%).

Table 6: Isolated pathogens from patients who used Accufuser® and their sensitivity

Antimicrobial agent	n (%)
Escherichia coli	30 (36.6%)
ESBL	27 (90.0%)
MR	1 (3.3%)
Staphylococcus spp.	18 (22.0%)
ESBL	1 (5.6%)
MRSA	7 (38.9%)
Klebsiella pneumoniae	10 (12.2%)
Panresistant	4 (40.0%)
ESBL	3 (30.0%)
Enterococcus spp.	5 (6.1%)
MR	2 (40.0%)
Candida spp.	4 (4.9%)
Pseudomonas aeruginosa	4 (4.9%)
MR	3 (75.0%)
Proteus mirabilis	3 (3.7%)
MR	3 (100%)
Total	97 (100.0)
Streptococcus spp.	2 (2.4%)
VZV	1 (1.2%)
Other anaerobic gram-negative	3 (3.7%)
Other gram positive	2 (2.4%)
Total	82 (100.0)

Accufuser® was used with a variety of antimicrobial agents, as illustrated in Table 7. Almost half of the patients were treated with carbapenems (45, 46.4%), mainly due to the high rate of resistance among the isolated organisms. Other antibacterial, antifungal, and antiviral agents were also administered successfully through Accufuser®.

Table 7: Antimicrobial agents that were used in the treatment of patients who used Accufuser®

Antimicrobial agent	n (%)
Carbapenems	45 (46.4)
Ertapenem	31 (32.0%)
Meropenem	13 (13.4%)
Imipenem	1 (1.0%)
Carbapenems	45 (46.4)
Tigecycline	8 (8.2%)
Vancomycin	5 (5.2%)
Tazocin	4 (4.1%)
Ampicillin	2 (2.1%)
Ciprofloxacin	2 (2.1%)
Augmentin	1 (1.0%)
Aztreonam	1 (1.0%)
Antifungal	7 (7.2%)
Cefazolin	8 (8.2%)
Ceftazidime	6 (6.2%)
Ceftriaxone	4 (4.1%)
Cefepime	1 (1.0%)
Anti-viral	3 (3.1%)
Acyclovir	2 (2.1%)
Ganciclovir	1 (1.0%)
Total	97 (100.0)

Discussion

HHC is a means of providing high-quality health care that is safe, cost-effective, and minimally invasive to patients' daily lives. Embracing new tools and devices is essential to ensuring the expansion of HHC and improving the quality of care. We assessed the use of the newly introduced device, Accufuser®, in the home parenteral antimicrobial program in the HHC Department at KAMC in Riyadh. We found that Accufuser® does not carry a significant risk of complications of therapy compared with other methods of IV administration. Accufuser® is superior to traditional methods in reducing the duration of visits and the frequency of daily visits. Thus, this new device allows nurses to visit more patients daily and accommodate patients within further distances. This effect is also supported by a systematic review that studied the use of elastomeric pumps in home IV antimicrobial programs [12].

We used Accufuser® to treat a variety of infections and administer a list of antimicrobials. It was most practical with medications that require slower administration or frequent daily doses without visiting the patient for each dose. Almost half of the patients were treated with carbapenems, given the high resistance seen among the isolated pathogens. This is in line with a finding in another study that evaluated home antimicrobial programs and found that carbapenems were the most commonly used agents [13].

Most of the complications observed were related to the use of PICC lines. None of the reported complications were specifically related to the Accufuser®; however, adherence to therapy may be questionable in patients who failed to improve. Nonetheless, those complications were not significant when compared to the complications reported with the use of other administration methods. Accufuser® can be used safely in patients with advanced age, cognitive impairment, DM, CKD, and medications with frequent daily doses. In a study that evaluated the use of elastomeric pumps in a university hospital in Switzerland, most of the complications observed were adverse reactions to the prescribed medications [14].

There is a paucity of research evaluating experiences of using electrometric pumps in home parenteral antimicrobial programs. Most studies have evaluated the use of those pumps in home chemotherapy and pain therapy programs. This can be attributed to the assumed stability issues of some antimicrobial agents. However, many studies have proven the stability of many agents in different elastomeric pumps [4], [5], [6], [7], [8], [9], [10]..

Conclusion

We believe that the Accufuser® device is a safe method of administering antimicrobial therapy at home. It significantly reduces the duration and frequency of visits. Taking this effect into account, further studies may be needed to evaluate the cost-effectiveness of this device. Further research to evaluate the experience of health care providers and patients (and their caregivers) may provide further insights as well regarding the impact of this device on the HHC program.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 May 20; 14(1):38-40.
https://doi.org/10.3889/oamjms.2026.12123
eISSN: 1857-9655
Category: *C – Case Reports*
Section: *Case Reports in Gynecology and Obstetrics*

Primary Echinococcus of the Ovary and Fallopian Tube. Case From Practice with Short Literature Review

Koni Vancho Ivanova[1], Mehmed Hadhzi[1], Ina Tzoneva[2]

[1]Department of General and Clinical Pathology, Trakia University, Faculty of Medicine, Stara Zagora, Bulgaria; [2]Clinic of Obstetrics and Gynecology - University Hospital "Prof. Dr. Stoyan Kirkovich", Stara Zagora, Bulgaria

Citation: Ivanova KV, Hadhzi M, Tzoneva I. Primary Echinococcus of the Ovary and Fallopian Tube. Case From Practice with Short Literature Review. Open Access Maced J Med Sci. 2026 May 20; 14(1):38-40. https://doi.org/10.3889/oamjms.2026.12042
Keywords: Echinococcosis; ovary and fallopian tube; case report
***Correspondence:** Koni Vancho Ivanova. Department of General and Clinical Pathology, Trakia University, Faculty of Medicine, Stara Zagora, Bulgaria. E-mail: koni_ivanova@yahoo.com
Received: 30-Jan-2026
Revised: 09-Feb-2026
Accepted: 11-Mar-2026

Funding: This work was supported by Bulgarian Ministry of Education and Science (MES) in the frames of Bulgarian National Recovery and Resilience Plan, Component “Innovative Bulgaria”, the Project № BG-RRP-2.004–0006-C02 “Development of research and innovation at Trakia University in service of health and sustainable well-being”.
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Echinococcosis is a helminthic disease caused by the development of the larval form of the echinococcal tapeworm in various human organs. The detection of an echinococcal cyst in the pelvic region, especially as a primary localization, is extremely rare, with literature data showing a frequency between 0.2 and 2.25%. Ovarian involvement is often a secondary dissemination of a cyst localized in a different location.

CASE REPORT: We present a 17-year-old girl with complaints of mild pain, heaviness in the small pelvis, and a cystic formation was detected by ultrasound examination.

CONCLUSION: Diagnosing this disease is extremely important for proper treatment. The possibility of a hydatid cyst should be kept under differential diagnosis while evaluating the cystic diseases of the ovary.

Introduction

Hydatidosis is a globally distributed zoonotic infection caused by the larval stage of cestodes of the genus Echinococcus, most commonly Echinococcus granulosus [1], [2], [3]. The disease remains endemic in regions where humans live in close proximity to livestock—particularly sheep, cattle, and dogs—facilitating the completion of the parasite’s life cycle.

Such geographical areas include the Mediterranean basin, Eastern Europe, the Middle East, East Africa, South America, and Australia [1], [2]. Humans become accidental intermediate hosts following ingestion of parasite eggs, after which hydatid cysts may develop in nearly any organ except the nails, hair, and cornea [4]. The liver is the most frequently involved site, accounting for approximately 60–63% of cases, followed by the lungs in about 25% of patients [4], [5], [6]. Less common localizations include muscles, bones, kidneys, the brain, and the spleen [7]. Pelvic involvement is rare, reported in only 0.2–2.25% of all cases and usually resulting from secondary dissemination from another primary organ [8]. Hydatid disease of the female reproductive system is exceptionally uncommon.

When present, the ovary constitutes the most frequently affected genital organ, followed by the uterus [9]. Primary ovarian echinococcosis, in which the ovary represents the initial site of infestation without hepatic or pulmonary involvement, is exceedingly rare and often clinically indistinguishable from benign or malignant ovarian cysts [3]. This diagnostic ambiguity highlights the importance of considering hydatid disease in the differential diagnosis of adnexal masses, particularly in patients from endemic regions.

Case report

We report a case of a 17-year-old patient admitted to the Obstetrics and Gynecology Clinic at the University Hospital "Prof. Dr. Stoyan Kirkovich" - Stara Zagora, with pain in the left lower abdominal quadrant, with a history of about 2 months. The gynecological examination and the ultrasound diagnosis revealed an

enlarged left ovary measuring 7/5.5 cm, with the presence of cystic formations with hypoechoic rounded shadows, surrounded by hyperechoic borders. The admitting diagnosis was a benign neoplasm of the ovary. All parameters from the routine blood tests were normal. Microbiologically no bacterial flora and candida were isolated.

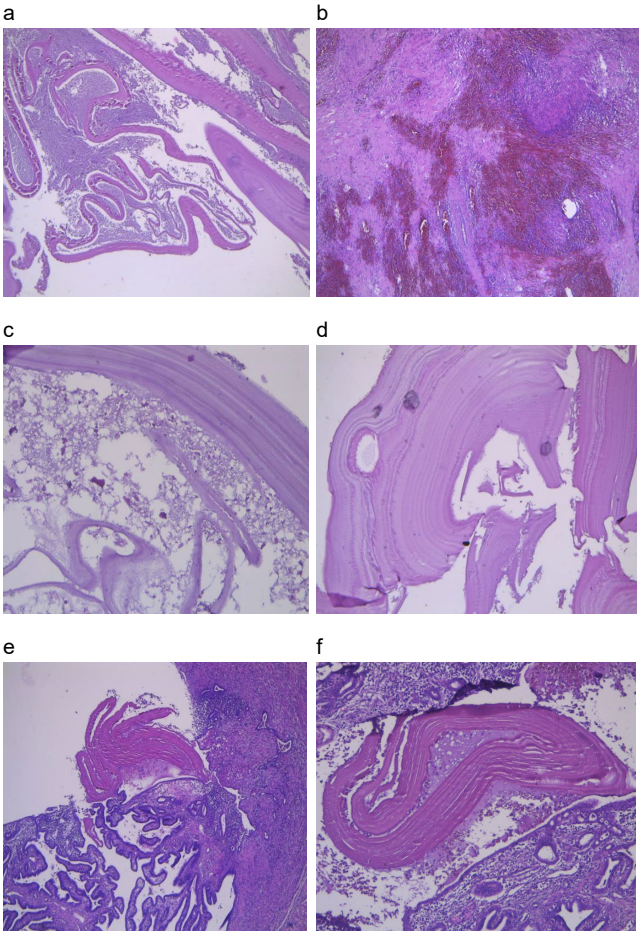

Figure 1: All slides are with HE staining x 100 magnification. We can see the chitinous membrane (a, c, d) the fibrous capsule in ovary (b) and the chitinous membrane in fallopian tube (e, f).

The microscopic examination revealed the presence of chitinous membranes, scolex, and fibrous capsule with hemorrhages, follicular cyst and corpus luteum. Chitin membranes and acute circulatory changes were found on the fallopian tube. The histological diagnosis was echinococcus of the ovary and fallopian tube (Figure 1).

Discussion

Primary ovarian echinococcosis remains one of the rarest presentations of Echinococcus granulosus infection. Pelvic localization accounts for only 0.2–2.25% of cases, and the ovary is uncommonly affected as a primary site without hepatic or pulmonary involvement [1], [2]. Most adnexal hydatid cysts described in the literature occur secondary to intraperitoneal dissemination or rupture of a hepatic cyst [10]. True primary ovarian disease, particularly with concomitant fallopian tube involvement, is a strikingly rare phenomenon with fewer than a few dozen well-documented cases worldwide.

The present case involving a 17-year-old girl adds to this limited pool of evidence. Adolescents rarely present with pelvic hydatidosis, and the clinical manifestations are usually nonspecific—ranging from intermittent lower abdominal or pelvic pain to menstrual disturbances or a palpable mass. Imaging modalities such as ultrasound and CT may reveal multiloculated cystic structures, but distinguishing hydatid cysts from other adnexal pathologies (e.g., benign cystadenomas, paraovarian cysts, endometriomas, or even tubo-ovarian abscesses) remains challenging due to overlapping radiologic characteristics [11]

Cases of primary ovarian hydatid disease in young patients have been sporadically documented, generally demonstrating similar diagnostic difficulties. Some authors report incidental discovery during surgery for presumed ovarian neoplasms, while others describe presentations with acute complications such as torsion or rupture. Involvement of the fallopian tube, as encountered in this case, has been described even more rarely, and typically correlates with local extension or common lymphovascular pathways.

The absence of cysts in the liver or lungs strongly suggests atypical dissemination. Proposed mechanisms include hematogenous spread by passing the hepatic and pulmonary filters, lymphatic transfer through pelvic lymphatic networks, or microscopic peritoneal seeding. In our patient, the lack of peritoneal lesions combined with isolated adnexal involvement supports hematogenous or lymphatic dissemination as the most plausible etiological route [12].

Surgery remains the preferred treatment for pelvic hydatid cysts, as complete excision prevents recurrence and avoids complications such as rupture, secondary echinococcosis, or anaphylaxis [13]. For reproductive-age patients, careful surgical techniques are vital to preserve fertility and avoid spillage of cyst contents. Adjunct antiparasitic therapy with albendazole is recommended pre- and/or postoperatively in selected cases to reduce recurrence risk [14].

This case underscores the need to maintain suspicion for echinococcosis when evaluating adnexal masses in patients from endemic regions—even in adolescents with isolated pelvic findings [1], [10]. Early recognition can prevent misdiagnosis, inappropriate treatment planning, or intraoperative complications. Furthermore, when hydatid disease is presented in unconventional sites, it illustrates the biological variability of the parasite's dissemination pathways and the importance of thorough systemic evaluation [8].

The symptoms of pelvic echinococcosis are nonspecific and may include abdominal pain, menstrual disorders, reproductive problems, as well as

urination distrubances, ot can also simulate polycystosis or malignant process [3], [14]. The difficulties that arise in making a correct diagnosis are due to the nonspecific clinical symptoms associated with atypical ultrasound and radiological tests, which only show that it is a cystic formation.

Conclusion

The presented case of primary ovarian and fallopian tube echinococcosis in a 17-year-old girl represents a rare but clinically significant diagnostic challenge. The symptoms of pelvic echinococcosis are nonspecific and may include abdominal pain, menstrual disorders, reproductive problems, as well as urination disturbances, or can also simulate polycystosis or malignant process.

The absence of hepatic or pulmonary involvement emphasizes the need to consider hydatid disease in the differential diagnosis of adnexal masses, especially in endemic settings In conclusion, the optimal treatment is total cystectomy, regardless of location, followed by anthelmintic therapy. It is important not to exclude an echinococcal cyst as a possible diagnosis. This case adds to the limited literature on primary pelvic hydatidosis and highlights the importance of heightened clinical awareness.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 May 25; 14(1):41-46.
https://doi.org/10.3889/oamjms.2026.12113
eISSN: 1857-9655
Category: *F – Review Articles*
Section: *Narrative Review Article*

Obesity, Insulin Resistance and Dysregulation of the mTOR Signalling Pathway in Hidradenitis Suppurativa

Ivana Tusheva[1], Irena Dimitrovska[1], Vesna Trajkova[1], Vesna Brishkoska-Boshkovski[2,3], Tatjana Ruskovska[3]

[1]Department of Dermatology, City General Hospital "8th September" Skopje, North Macedonia; [2]Department of Dermatology, Acibadem Sistina Clinical Hospital, Skopje, North Macedonia; [3]Faculty of Medical Sciences, Goce Delchev University, Shtip, North Macedonia

Citation: Tusheva I, Dimitrovska I, Trajkova V, Brishkoska-Boshkovski V, Ruskovska T. Obesity, Insulin Resistance and Dysregulation of the mTOR Signalling Pathway in Hidradenitis Suppurativa. Open Access Maced J Med Sci. 2026 May 25; 14(1):41-46. https://doi.org/10.3889/oamjms.2026.12042
Keywords: hidradenitis suppurativa; obesity; insulin resistance; IHS4; mTOR; metformin
***Correspondence:** Ivana Tusheva. Department of Dermatology, City General Hospital "8th September" Skopje, North Macedonia. E-mail: tusevaivana@yahoo.com
Received: 06-Nov-2025
Revised: 01-Mar-2026
Accepted: 29-Mar-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent painful nodules, abscesses, and draining tunnels, with a predilection for intertriginous regions.

AIM: We aimed to review dysregulation of mTOR signalling pathway based on the latest relevant scientific studies.

METHODS: This literature review explores the association between HS, obesity, insulin resistance, and the dysregulation of mTOR signalling pathway. Additionally, research investigating the effects of therapeutic strategies, such as metformin and its influence on clinical outcomes in HS patients, was analyzed.

RESULTS: Obesity is considered a predisposing factor for the development of insulin resistance and type 2 diabetes, both of which influence the IHS4 (International Hidradenitis Suppurativa Severity Score System) score in HS patients. The prevalence of insulin resistance among HS patients is 43.4%. Studies have shown that metformin significantly reduces inflammatory cytokines, chemokines, and the expression of genes associated with glycolytic processes. In vitro analyses suggest that these effects are mediated through the modulations of the NLRP3 inflammasome and mTOR signalling pathway.

CONCLUSION: A holistic approach to HS treatment, including the management of obesity and insulin resistance, significantly improves disease progression. The use of metformin as an adjunct therapy in standard treatment protocols has the potential to improve IHS4 scores in obese patients.

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory and often severe skin disease that affects the hair follicles. HS usually presents after puberty with painful, deep, inflamed lesions in areas containing apocrine glands, most commonly under the armpits, inguinal and anogenital regions. The disease is recurrent, with at least two manifestations within a six-month period or with one or more chronic lesions lasting more than three months [1], [2].

The most commonly used scores for HS diagnosis and monitoring are Hurley (Hurley I, II and III) and IHS4 (International Hidradenitis Suppurativa Severity Score System). IHS4 score is obtained by the sum of the number of nodules (multiplied by 1), the number of abscesses (multiplied by 2) and the number of draining tunnels (multiplied by 4). A total score of 3 or less indicates mild disease, 4-10 moderate disease, and 11 or more severe disease [3]. The Sartorius score is also commonly used [4]. Recent studies have defined three stages in the pathogenesis of the disease: non-inflammatory, acute inflammation, and chronic inflammation [5].

The association of obesity and metabolic disorders with HS is well known. Both conditions lead to a chronic low-intensity systemic inflammation, so it is not clear whether the inflammation caused by metabolic disorders leads to the initiation of HS or whether the systemic inflammation in HS leads to the manifestation of metabolic disorders. This literature review aims to evaluate the metabolic disorders present in HS patients, the impaired metabolic molecular mechanisms that are directly correlated with the severity of the disease, as well as the therapeutic effects of metformin as a direct regulator of insulin

resistance, which underlies all these metabolic disorders.

Risk factors for the development of hidradenitis suppurativa in the Republic of North Macedonia

In 2023, a study was conducted in the Republic of North Macedonia, Skopje, which demonstrated a prevalence of HS of 0.84%, in a population of 598 participants [6]. The study later became part of a meta-analysis that included data from 23 countries on 6 continents with a total of 22,743 participants. This meta-analysis showed a global prevalence of HS of 0.99%, ranging from 0.67 – 1.46%, a finding that justifies the increased interest in this disease [7].

Although there are studies that indicate a genetic predisposition to the disease, two main risk factors that influence the development and course of HS have emerged, namely smoking and obesity. The presence of HS is more common in obese people compared to the general population, and losing more than 15% of body weight is associated with a significant reduction in the severity of the disease [8].

The interest in studying the prevalence of obesity in the Republic of North Macedonia is increasing. A cross-sectional study was conducted in 2022 which analyzed the prevalence of overweight and obesity in 1034 healthy children aged 6 to 13 years in the Republic of North Macedonia. The results showed that 57% of the children were of normal weight, 19.5% were obese, and 13.5% were overweight. The study showed a worrying increase in the rate of overweight and obesity, especially among the groups of children aged 6-7 and 8-9 years, where the rates increased from 17.9% to 25.4% for obesity and from 5.8% to 12% for overweight. The Global Atlas of Childhood Obesity predicts that the rate of obesity in children aged 5 to 19 in North Macedonia will increase up to 52.5% by 2030 [9].

Increased body weight in childhood leads to the early development of insulin resistance, metabolic syndrome and type 2 diabetes mellitus. Statistical analysis regarding the prevalence of diabetes in the Republic of North Macedonia is presented in a retrospective study, based on adult population data from the State Statistical Office for the period 2015-2019. The results showed a constant increase in the number of patients with diabetes. The number of registered patients increased from 103,480 in 2015 to 124,450 in 2019, showing an increase of 20.3%. The majority (95%) of these patients are diagnosed with type 2 diabetes (T2DM), while only 4.1% have type 1 diabetes (T1DM), indicating that T2DM is the dominant form of diabetes among the population. The prevalence increased from 5.66% in 2015 to 7.2% in 2019, showing an increase of 1.54% (an increase of 27%). This indicates a significant increase in the population diagnosed with T2DM [10].

Although there is evidence that the rising prevalence of childhood overweight and obesity increases the risk of developing type 2 diabetes later in life, nationally representative epidemiological data in the Republic of North Macedonia specifically linking childhood obesity with subsequent diabetes are currently lacking. Given the known associations between obesity and inflammatory skin disorders, it is relevant to explore whether similar trends exist for hidradenitis suppurativa (HS). However, there is currently a lack of epidemiological data assessing the prevalence or temporal trends of HS in the country.

Insulin resistance in hidradenitis suppurativa

Obesity is the most common cause of insulin resistance (IR). IR is defined as a decreased sensitivity of cells to insulin, resulting in reduced glucose uptake by muscle cells, increased glucose production by the liver, and increased lipolysis in the adipose tissue. This leads to increased insulin secretion and hyperinsulinemia, to maintain the normal functions of insulin. Insulin resistance is closely related to metabolic syndrome; in fact, it is one of its criteria. Other criteria that define metabolic syndrome include central obesity, hypertension and dyslipidemia [11].

In everyday practice, IR can be determined by several methods, the most accurate of which is the “hyperinsulinemic-euglycemic clamp” method, while the most commonly used is the homeostatic model assessment for insulin resistance (HOMA-IR) due to its simplicity of implementation [12]. HOMA-IR is determined by the product of the fasting glucose level and the fasting insulin level, divided by a constant (normalizing factor) [13].

Another method for assessing insulin resistance, which is widely used, is the triglyceride-glucose (TyG) index [14]. This index is considered superior to HOMA-IR for predicting metabolic syndrome and IR [15], because the first parameter whose concentration increases as a result of IR and cellular metabolic burden is the level of circulating triglycerides, which are predominately carried by chylomicrons and very low density lipoproteins (VLDL). In conditions of hyperglycemia and IR, VLDL production and chylomicron release increase, which leads to an increase in serum triglyceride levels. On the other hand, in IR and type 2 DM, increased hepatic gluconeogenesis leads to increased hepatic glucose production, thus increasing blood glucose levels. The association between increased triglyceride and glucose levels in insulin resistance is the basis for using both parameters (included in the TyG index) for assessment of various abnormalities associated with impaired insulin sensitivity [14].

IR (via HOMA-IR) is an independent risk factor for the development of metabolic dysfunction-associated steatohepatitis (MASH, formerly named as nonalcoholic fatty liver disease). In fact, HOMA-IR is a

potential indicator of the risk of developing MASH in non-diabetic and non-obese patients and can be used in the diagnosis of the disease and as a screening method [16]. There is a strong association between MASH and HS, namely patients with hidradenitis suppurativa have a significantly higher prevalence of MASH (57.6%) compared to those without HS (31.7%), regardless of the presence of traditional metabolic risk factors such as age, body weight, hypertension and elevated levels of circulating transaminases [17], [18].

IR and type 2 DM are among the most common comorbidities in patients with HS [19]. Patients with HS have a higher risk of developing IR compared to healthy individuals, as 43.4% of HS patients have IR compared to only 16.4% in the control group [20]. The prevalence of type 2 DM in patients with HS is significantly higher than in healthy individuals (39% vs 19%) [21]. In addition, HS is associated with other metabolic disorders, including hypertriglyceridemia (OR 1.67, 95% CI 1.14–2.47, P =0.009), low values of high-density lipoprotein (HDL) (OR 2.48, 95% CI 1.49–4.16, P <0.001), diabetes (OR 2.85, 95% CI 1.34–6.08, P =0.007), and metabolic syndrome (OR 2.22, 95% CI 1.62–3.06, P <0.001) [22].

HS patients exhibit heterogeneity of metabolic disorders, but essentially all of them are based on dysregulation of the mTOR signalling pathway that govern the metabolic processes at the cellular level.

mTOR signalling pathway, metabolic disorders, and hidradenitis suppurativa

mTOR or mammalian target of rapamycin is a 289 kDa serine/threonine protein kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related protein kinase family. mTOR consists of two distinct multi-protein complexes known as mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). These complexes differ in their structure, sensitivity to rapamycin, and specific functions. The mTOR pathway integrates a diverse set of signals, such as signals from growth factors and nutritional status, and determines the direction in which eukaryotic cells will grow, depending on whether it activates anabolic or catabolic processes. mTORC1 is sensitive to nutrients (amino acids, glucose), energy (ATP levels), and growth factors (insulin, IGF-1) and controls protein synthesis, lipid metabolism, and autophagy. mTORC2 responds mainly to growth factors and regulates cytoskeletal organization, cell survival, and insulin signalization. Given the central role of this pathway in maintaining cellular and systemic homeostasis, dysregulation of mTOR signalling has been linked to metabolic disorders, neurodegenerative diseases, cancer, and aging [23], [24].

Liu and Sabatini (2020) describe the role of mTOR signalling in the development of IR. Obesity, caused by overfeeding, creates a large and harmful energy imbalance in the body. This leads to a continuous excess of hormones, cytokines, and nutrients, disrupting the metabolic cycles responsible for cellular homeostasis, placing mTORC1 in a persistently active state. Under these conditions, constitutive mTORC1 signalling activates S6K1 and Grb10 to uncouple the insulin/IGF-1 receptor from downstream effectors of the PI3K pathway, leading to a reduced physiological response to insulin. In addition, PI3K inhibition suppresses the mTORC2-Akt axis, which blocks glucose uptake and promotes gluconeogenesis, further increasing glycemic load and exacerbating ectopic fat deposition and glucose intolerance [25].

Accordingly, medications that counteract these mechanisms may be beneficial in reducing body weight and improving insulin sensitivity and type 2 diabetes mellitus. Metformin finds its application in this area as an already well-known and widely used drug for type 2 DM, by effectively suppressing mTORC1 through both AMPK-dependent and AMPK-independent mechanisms, depending on the dose, and thereby improving insulin sensitivity [26].

Meta inflammation and hidradenitis suppurativa

Meta inflammation is a term first introduced by Gökhan S. Hotamisligil, and it refers to chronic, low-grade systemic inflammation driven by metabolic disorders. Meta inflammation is characterized by only a moderate increase in circulating proinflammatory factors and the absence of clinical signs of inflammation (subclinical inflammation). The main factors that drive this inflammation are excessive fat deposition, insulin resistance and impaired immune signalling (chronic inflammation) [27].

Meta inflammation affects the metabolic organs, with a main emphasis on adipose tissue. Adipose tissue is a histologically diverse structure composed of mature adipocytes, preadipocytes and a stromal-vascular component that includes vascular endothelial cells and various immune cells from the innate and adaptive immune systems. Functionally, adipose tissue serves as an energy store, an endocrine organ, and an important factor in immunological regulation [28].

Under conditions of continuous excessive food intake, changes occur in the number and activity of almost all resident immune cells in the adipose tissue. Additionally, various subsets of immune cells are recruited. The imbalance in immunological phenotypes leads to the development of local inflammation and the release of biologically active components that enter systemic circulation [29].

Macrophages and lymphocytes represent the most abundant immune populations in the white adipose tissue. Depending on the degree of obesity, adipose tissue macrophages (ATMs) exhibit different phenotypes. In lean, non-obese individuals, ATMs have anti-inflammatory activity (M2 macrophages),

whereas in obese individuals, as a consequence of excessive triglyceride accumulation, they express pro-inflammatory genes (M1 “classically activated” macrophages) [30]. Pro-inflammatory cytokines produced by M1 ATMs (for example, TNFα or IL6) promote adipocyte hypertrophy, which further leads to the release of cytokines and chemokines that amplify and maintain adipose tissue inflammation, causing systemic inflammation through a positive feedback loop [31].

Adipose tissue is an endocrine organ that regulates a multitude of physiological processes through the mediation of chemokines, known as adipokines. Adipokines have emerged as key regulators of inflammation. Leptin and resistin are considered pro-inflammatory adipokines, while adiponectin is considered an anti-inflammatory adipokine. Mean serum adiponectin levels are significantly reduced in patients with HS, while serum resistin and leptin levels are significantly elevated compared to healthy individuals [32], [33].

Metabolic syndrome and HS share the same adipokine profile (HS-MetS adipokine profile) and significantly overlap in the activity of inflammatory pathways [34].

There are still not precisely defined clinical biomarkers for this low-grade systemic inflammation. Relevant indicators could be CRP, especially the high-sensitivity method, as well as cellular biomarkers such as leukocytes and platelets [35].

Metformin and hidradenitis suppurativa

Metformin is an oral biguanide approved for the treatment of type 2 diabetes [36]. By its mechanism of action, metformin is an activator of adenosine monophosphate-activated protein kinase (AMPK) and an mTORC1 inhibitor [37]. Hepatocytes are the main site of action of metformin, where it regulates hepatic glucose production. However, an increasing number of studies indicate that metformin may have additional sites of action, including the gastrointestinal tract, intestinal microflora, and tissue-resident immune cells. In addition, the use of metformin in various pathophysiological conditions is expanding [38].

One of the mechanisms by which metformin improves the clinical findings in HS is through its direct action on insulin resistance and meta inflammation. In a case-control study of 40 patients with HS (20 on metformin therapy for at least 6 months and 20 without metformin therapy in the last 6 months), there was a significant reduction in biomarkers of cardiovascular disease risk in the group that takes metformin (lymphocytes, monocyte-lymphocyte ratio, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio). Also, in the same study, a decrease in fasting insulin and a trend towards a decrease in insulin resistance (HOMA-IR) were observed in the group who took metformin over 6 months. CRP was also lower in the metformin group, but without statistical significance [39].

In order to detect the immunometabolic effects of metformin in patients with HS, a comparative analysis of peripheral blood mononuclear cells (PBMCs) from metformin-treated and untreated patients was performed, which showed an improvement in deregulated metabolic pathways and a decrease in inflammatory markers after a long-term metformin therapy. An ex vivo HS lesion model showed that metformin reduces inflammatory cytokines, chemokines, and glycolytic gene expression in lesions in patients with HS. In vitro analyses further suggest that these effects are mediated through the NLRP3 inflammasome and the AMPK-mTOR signalling pathway, which regulates glycolysis and protein synthesis [40].

To our knowledge, there are very few studies on the effects of metformin on keratinocytes. Under normal conditions, mTORC1 activity is suppressed when keratinocytes progress from proliferation to terminal differentiation. However, in inflammatory conditions, cytokines such as IL1β, IL17A, and TNFα excessively stimulate mTORC1 activity, leading to excessive keratinocyte proliferation and impaired differentiation. Metformin helps restore the balance by inhibiting mTORC1 activity, mainly through the activation of AMP-activated protein kinase (AMPK). This inhibition of mTORC1 restores normal keratinocyte differentiation and modulates key transcription factors such as the hypoxia-inducible factor HIF-1α and the signal transducer and activator of transcription STAT3. STAT3, together with HIF-1α, activates glycolysis and inflammatory responses, which are reduced when metformin blocks the mTORC1 signalling pathway [41].

Metformin treatment significantly reduces the severity of the disease, wherein 76% of patients show improvement in Sartorius score and almost half progressed from severe to mild/moderate HS. Additionally, the quality of life has improved in 64% of patients, with a reduction in DLQI score of more than 50%, and the number of lost work days decreased from 1.5 to 0.4 per month [42]. Another study showed improvement in the disease in 68% of patients after six months of metformin therapy, while 19% of them had complete remission with metformin as monotherapy [43].

Conclusions

The rate of obesity and overweight in children in the Republic of North Macedonia is on the rise, potentially contributing to an increase in the number of diagnosed cases of diabetes in adulthood. Although there is a lack of relevant epidemiological studies that would confirm an increase in the number of patients with HS, the close correlation between obesity and the development of this disease suggests that primary

prevention should focus on nutrition in childhood and the promotion of maintaining optimal body weight.

Obesity is a key factor in the development of metabolic disorders in patients with HS, which most often include insulin resistance (IR), hypertriglyceridemia, metabolic syndrome, metabolic-associated steatohepatitis (MASH) and type 2 diabetes (type 2DM). Although there is considerable heterogeneity of metabolic disorders in patients with HS, basically all of them are associated with dysregulation of mTOR signalling pathway, which plays a central role in cellular metabolic regulation.

Patients with HS exhibit serum proinflammatory biomarkers similar to those observed in meta inflammation. Chronic inflammation in HS can worsen metabolic disorders, while low-grade metabolic inflammation complicates the clinical findings of HS, creating a vicious circle (circulus vitiosus).

The promotion of a healthy lifestyle and maintaining optimal body weight from an early age are key preventive measures against the disease. Weight reduction can have a significant positive impact on the course of the disease.

The introduction of metformin therapy is recommended for obese patients with HS and metabolic disorders, which is applied in parallel with the standard therapeutic protocol.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 May 23; 14(1):47-52.
https://doi.org/10.3889/oamjms.2026.12134
eISSN: 1857-9655
Category: *B – Clinical Sciences*
Section: *Hematology*

Distribution, Severity and Mortality of COVID-19 in Relation to Blood Group and Rh Factor

Gazmend Amzai[1*], Milena Srbinoska-Bogatinoska[2], Oliver Karanfilski[1], Glorija Stefanoska-Tosheska[3], Tatjana Kjosevska[4], Eleonora Grozdanova[5], Argjent Muca[6], Tatjana Proseva[6], Lidija Poposka[7], Marija Dimzova[8]

[1]University Clinic for Hematology, Medical Faculty, Ss Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia; [2]Health Center Makedonski Brod, Republic of North Macedonia; [3]General Hospital, Prilep, Republic of North Macedonia; [4]Health Center Shtip, Republic of North Macedonia; [5]General Hospital, Kochani, Republic of North Macedonia; [6]University Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Medical Faculty, Ss Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia; [7]University Clinic for Cardiology, Medical Faculty, Ss Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia; [8]University Clinic for Infectious Diseases and Febrile Conditions, Medical Faculty, Ss Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia

Citation: Amzai G, Srbinoska-Bogatinoska M, Karanfilski O, Stefanoska-Tosheska G, Kjosevska T, Grozdanova E, Muca A, Proseva T, Poposka L, Dimzova M. Distribution, Severity and Mortality of COVID-19 in Relation to Blood Group and Rh Factor. Open Access Maced J Med Sci. 2026 May 23; 14(1):47-52. https://doi.org/10.3889/oamjms.2026.12134
Keywords: COVID-19; ABO blood group system; Rh
***Correspondence:** Gazmend Amzai, University Clinic for Hematology, Medical Faculty, Ss Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia
Phone: +38970251082
E-mail: dr.gazmend_amzai@hotmail.com
Received: 03-Mar-2026
Revised: 04-Apr-2026
Accepted: 29-May-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: During the Covid-19 pandemic, a number of investigators reported that in patients with different blood groups the virus had a disparate influence regarding the severity and the outcome of the infection.

AIM: The goal of our study was to determine if there is an association between blood groups and Rh factor regarding the severity and mortality from COVID-19 in our analyzed patient population.

METHODS: We conducted a retrospective observational study of 250 patients with COVID-19 disease, treated as ambulatory or hospitalized patients in several health facilities during a time period of one year, from November 2020 till November 2021.

RESULTS: The majority of patients in our cohort were confirmed to have blood group A - 115 (46%), followed by blood group O - 67 (26.8%) patients, 45 (18%) patients were with blood group B, and 23 (9.2%) patients were with blood group AB. The data generated from our analysis revealed a higher than standard prevalence of SARS-CoV-2 infections among individuals with blood group A. Also, the analysis shows that patients with blood group A experience a more severe clinical course of the disease, as well as higher mortality, compared to patients with other blood groups. There is a substantial difference between Rh positive and Rh negative patients in terms of the severity of the disease. Rh positive patients more frequently experience a severe clinical course, confirmed by statistical significance, but the Rh factor does not affect the outcome of the infection.

CONCLUSIONS: The results from our analysis showed that patients with blood group A manifest a more severe clinical course of the disease and a higher mortality rate compared to patients with other blood groups, but statistical significance between them could not be documented.

Introduction

Corona virus disease (COVID-19) represents a public health risk of global proportions that causes substantial morbidity and a considerable burden of mortality that has overwhelmed health systems worldwide [1]. It has been recognized that SARS-CoV-2 virus attacks the organs and tissues of the human body through the ACE receptors located on the cell surface [2]. While a large proportion of infected patients express no symptoms, some patients experience moderate symptoms and in some patients the disease may progress to pneumonia, hypoxemia, severe respiratory distress syndrome and multiple organ failure, potentially leading to death. No physiological biomarker can accurately predict COVID-19 susceptibility, but ABO blood group has been reported to be correlated to the propensity of the SARS-CoV-2 infection.

It is thought that blood group antigens play a direct role in the infection through various mechanisms. On a molecular level, they can serve as receptors and co-receptors for pathogens and can also facilitate intracellular uptake of viral particles. Clinically, blood

groups have been linked to bacterial, parasitic, viral infections and various non-infectious diseases [3], [4], [5], [6], [7], [8].

The blood groups are defined by the presence of specific carbohydrate sugars on the surface of blood cells. The ABO antigens were later found in several tissues and secretions, such as saliva, intestinal mucosa and the respiratory tract epithelium. It is assumed that the influence of ABO blood groups regarding the susceptibility towards and the severity of COVID-19 infections are regulated by mechanisms of interaction between ABH antigens and sialoside glycans present on the host cell receptors [9].

During the most immense peaks of the pandemic, genotype analyses were performed in large patient populations with severe SARS-Cov-2 infections, revealing specific genomic loci coinciding with the ABO group locus. Statistical analyses confirmed existence of a higher risk of infections in individuals of the A blood group, as well as a protective role of the O blood group [10].

Meta-analyses were also performed, aimed at establishing associations between ABO phenotypes and various mechanisms of organ and system failures caused by the SARS-Cov-2 infection. Demographics were considered as possible means of preventing outbreaks within environments containing populations with different ratio coefficients regarding the blood groups [11].

The issue of different ratios and frequencies of blood groups in different populations, especially in different geographical locations, has been analyzed and observations have been associated with variations in overall susceptibility of a nation, region, or even continent towards certain types of infections, sometimes even diseases in general [12]. Therefore, when attempting to establish a specific link between a medical observation and an individuals' blood group, a certain degree, level of a demographic and population statistic overview is warranted.

The reports and derived conclusions regarding the role of ABO blood groups in the pathogenesis of COVID-19 infections are still controversial. Initial studies have observed no association between ABO blood groups and SARS-CoV-2 infection [13]. However, a considerable number of later studies showed that ABO polymorphism was associated with susceptibility to SARS-Cov-2 infection, indicating that blood type A and Rh positivity were risk factors regarding the severity of COVID-19 infection as well as the consecutive rate of mortality [14], [15].

Since the issues are not defined on a general level, our study was aimed at determining if there is an association between blood groups and the Rh factor in our patient population, when analyzed against the prevalence, as well as the severity and clinical outcomes of COVID-19 infections. The establishment of a correlation between blood types and the course of COVID-19 infections would be our contribution to the challenging problem and within a global assessment framework could lead to the development of clinically applicable strategies, guiding disease management and treatment in eventual future outbreaks.

Methods

We conducted a retrospective observational study of 250 patients with COVID-19 disease treated as outpatients or as hospitalized cases in several health facilities in the Republic of North Macedonia: Health Center Makedonski Brod, General Hospital Prilep, Health Center Shtip, General Hospital Kocani and the modular hospital at the University Clinic for infectious diseases and febrile conditions in Skopje, during a time period of one year, from November 2020 till November 2021. All patients had positive SARS-CoV-2 RT-PCR swabs and were older than 18 years. For all patients included in the study we collected data related to demographic characteristics, date of SARS-CoV-2 positive test, ABO blood group and Rh type, as well as medical data characterizing the severity of the COVID-19 infection.

We classified the patients according to the CDC classification of disease severity into three groups: 1. mild illness (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell), 2. moderate illness (patients with evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 ≥94% on room air at sea level), treated as outpatients and 3. severe illness (patients with SpO_2 <94% on room air at sea level, PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%) which required hospitalization. None of the patients included in the study were previously vaccinated.

ABO blood group and Rh type were determined either at initial clinical evaluation or were extracted from the system of electronic data for the respective patient. ABO blood groups and Rh types were determined at the Institute for transfusion medicine of the Republic of North Macedonia.

The frequencies of the blood groups among our patients are subject of the analysis in various comparator modalities, matched against the population standard. The frequency of the ABO phenotype in the Republic of North Macedonia is as follows: O blood group 33%, A 41%, B 18% and AB 8% of the population, as reported and documented by the national statistics in 2021 [16].

Statistical analysis of the data was performed using the statistical program SPSS 23.0. Categorical (attributive) variables are shown with absolute and relative values. The non-parametric Chi-square test was used to compare the categorical variables. $P<0.05$ was considered statistically significant. The data are presented in tables and graphics.

Results

Patient characteristics

Among the 250 subjects included in the study, 115 were male and 135 were female. The average patients' age was 51.3 years and 143 of them were older than 50 years (Table 1).

Table 1: Demographic characteristics of the patients

Parameter	n (%)
Gender	
female	115 (46)
male	135 (54)
Age group	
<49	107 (42.8)
≥50	143 (57.2)
Age/years (mean ± SD)	51.3 ± 16.4

Blood group distribution among patients

The majority of our patients were identified as having blood group A – 115, followed by blood group O - 67 patients, 45 patients were with blood group B, and 23 patients had blood group AB. (Figure 1) Compared to the standard distribution of blood groups in the general population, the analysis shows a misbalance, which is mainly due to the contrasted presence of individuals with blood group A (higher) and O (lower).

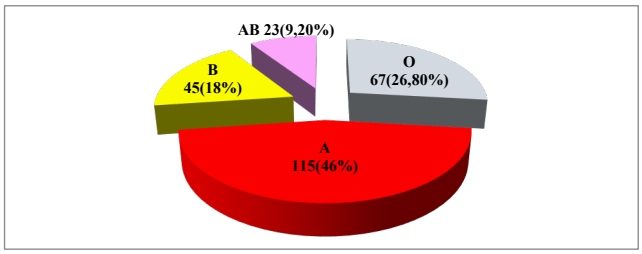

Figure 1: Proportion of patients according to blood group

The blood groups were proportionally distributed across different gender and age groups (p>0.05).

Among the patients that acquired a COVID infection, those having blood group B maintained the proportion size comparable to the general population. Patients with blood group O were represented in a smaller proportion than in the general population, delineating a possible lower susceptibility to the viral agent.

Table 2: The blood group of the patients in relation to gender and age

Variable		Blood group					p-value
		n	O n (%)	A n (%)	B n (%)	AB n (%)	
gender	female	115	29 (25.22)	55 (47.83)	20 (17.39)	11 (9.56)	X^2=0.4
	male	135	38 (28.15)	60 (44.44)	25 (18.52)	12 (11.1)	p=0.9
Age group	<49	107	29 (27.1)	46 (42.99)	20 (18.69)	12 (11.21)	X^2=1.2
	≥50	143	38 (26.57)	69 (48.25)	25 (17.48)	11 (7.69)	p=0.74
Standard distribution (national data)			33%	41%	18%	8%	

X^2, (Chi-square test).

In accordance with the reported higher susceptibility regarding patients with blood group A, our patients were represented with a margin from 3-7% higher than the ordinary, and those with blood group AB were within a range of 1.5-3% above the standard (Table 2). The most noticeable proportion increase is among the elderly patients with blood group A.

The blood group of the patients in relation to the clinical course severity and outcome

There is an easily detectable trend of increase in the severity of the disease in the patient population having blood group A, and partially (moderate severity) for patients with group AB. For patients with blood group O and B there is a stable or clearly declining trend regarding severity. This undoubtedly confirms the greater gravity of the consequences of the COVID infection among patients bearing the A blood group antigen. The proportion of fatal outcomes also confirms this connection, since patients with blood group A constitute for more than half of the fatalities, while patients with the other blood groups retain a positive or stable ratio between surviving and deceased patients (Table 3).

Table 3: The blood group of the patients in relation to the clinical course severity and mortality

Variable		Blood group					p-value
		n	O n (%)	A n (%)	B n (%)	AB n (%)	
Clinical course	Mild	103	32 (31.07)	42 (40.78)	20 (19.42)	9 (8.73)	X^2=4.2
	Moderate	43	9 (20.93)	20 (46.51)	8 (18.6)	6 (13.95)	p=0.65
	Severe	104	26 (25)	53 (50.96)	17 (16.35)	8 (7.69)	
Outcome	Survived	223	61 (27.35)	100 (44.84)	40 (17.94)	22 (9.87)	X^2=1.8
	Deceased	27	6 (22.22)	15 (55.56)	5 (18.52)	1 (3.7)	p=0.61

X^2, (Chi-square test).

The Rh factor in patients in relation to the disease severity and mortality

Patients with positive and negative Rh factor differed significantly in terms of the severity of the clinical course of the disease, as well as regarding the outcome (p=0.0021). Almost all patients with a severe disease course were with a positive Rh-factor. As expected, all of the fatal outcomes are noted in the Rh-positive patient population, while among Rh-negative patients no fatalities were observed (Table 4).

Table 4: The Rh factor in patients in relation to the disease severity and mortality

Variables		Rh factor				p-value
		n	positive n (%)		negative n (%)	
Clinical picture	Mild	103	91 (88.35)		12 (11.65)	X^2=12.3
	Moderate	43	35 (81.4)		8 (18.6)	**p=0.0021
	Severe	104	102 (98.08)		2 (1.92)	
Outcome	Survived	223	201 (90.13)		22 (9.87)	X^2=2.9
	Deceased	27	27 (100)		0	p=0.087

X^2, (Chi-square test).

Discussion

There are many studies which have investigated the connection between COVID-19 and blood types, and they all convey a variable level of differences in their assessments [17], [18]. Almost 20

years ago, Cheng and associates have noted the association between blood groups and susceptibility to SARS-CoV-1 infections, stating that individuals of blood type O are at lower risk of acquiring the disease [19].

Further trials revealed a protective effect of anti-A antibodies against intracellular uptake of SARS-CoV-1 [20].

These observations have led researchers to investigate whether an association exists between ABO polymorphism and susceptibility to SARS-CoV-2 infection.

In our study the majority of COVID-19 patients were with blood group A. They developed a more severe clinical course of the disease, and the mortality was higher in this blood type, compared to other types, as well as to the standard blood group distribution. In the study of Zhao and associates there was a similar observation as in our cohort of patients. Namely, their study showed that the majority of COVID-19 patients had blood type A and the highest affinity for bonding with the SARS-CoV-2 virus, contrary to patients with blood type O who had the lowest bonding affinity [14]. As reported before, the highest prevalence of a severe clinical disease course in our study is noted among individuals with blood group A. This blood type is also accountable for the highest proportion of fatal outcomes. On the other hand, individuals with blood type O and B (to some extent) bear a lower risk burden for developing a severe disease course, as well as for progressing to a fatal outcome, while those with the AB blood type are with a relatively "standard" prevalence, which substantially corresponds to the findings of Matzhold and associates [21].

Among relevant medical literature exploring and evaluating different databases, most reports confirm a significantly increased risk of infection in individuals with blood group A and a low risk in those with blood group O [18], [22], [23].

There are many hypotheses which can explain our findings and the most constant among them state that the presence or absence of any antigen of the ABO system is responsible for a different degree of susceptibility, also confirming that comorbidities are substantially more frequent in patients with antigen A (A blood group), while the absence of antigens (O blood group) is associated with a lower thrombotic and cardiovascular risk [24], [25].

Initial attempts to explain the observations connecting blood groups with the intensity of SARS-CoV-2 infections, were unable to document a direct molecular relationship between the ABO system antigens and the virus that could explain the true mechanism responsible for the susceptibility of individuals with different blood groups. Natural anti-A and anti-B antibodies from the ABO system were labeled as capable of interfering with the S protein of the SARS-CoV-2 virus and with the angiotensin-converting enzyme 2 on the host cell receptors. The presence of high plasma concentrations of antibodies in the O blood group was presumed to confer greater protection to these patients [26].

Many similar reports to our study, although documenting discrepancies regarding the severity of the disease and the outcome of the infection analyzed against different blood types and Rh-factors, did not succeed in establishing a statistical significance regarding the clinical outcomes of COVID-19 infections and the different ABO blood groups [27[, [28], [29].

More recently, Wu et al. documented that structural and sequence analogies exist within the receptor-binding domain of the surface spike protein of the SARS-CoV-2 virus and a certain carbohydrate-binding protein family called galectins, which accounts for the similarities in glycan-binding preferences. Galectins manifest a considerable affinity towards ABO(H) antigens and engage them. In particular, a specific one, labeled galectin-4C, expresses affinity towards blood group A structures found also on respiratory epithelial cells. On the contrary, no affinity was documented against the H antigen, present in blood group O, therefore concluding that a greater susceptibility exists for blood group A cells, than O cells, to be infected with the SARS-CoV-2 virus, and providing a molecular background for that observation [30]. Although on different levels, the study confirmed that the affinity persists among different strains of the virus.

In the study of Young and associates it was shown that Rh negative patients have a lower risk for acquiring COVID infection, but the Rh factor had no influence on the outcome of the disease. Our study showed similar findings, namely that the Rh positive patients in our cohort presented with a more severe clinical course compared to Rh negative patients, but this finding did not achieve statistical significance regarding the disease outcomes [17]. Our analysis, similar to the studies of Ray et al. and Zietz et al., found that subjects with Rh-negative blood type were at lower risk of viral infection, severe illness course, and mortality following a SARS CoV-2 infection [31], [32], [33]. Nevertheless, the results of these studies were affected by some limitations, such as selection bias for inpatient hospital population due to limited testing and moderate sample size. Greater sample sizes and meta-analyses are required in order to evaluate and elaborate the essence of these observations with more substantial precision.

Conclusions

The results from our analysis showed that patients with blood group A manifest a more severe clinical course of the disease and a higher mortality rate compared to patients with other blood groups, but statistical significance between them could not be documented. There is a substantial difference between

Rh positive and Rh negative patients in terms of the severity of the disease. Rh positive patients often have a more severe clinical course, which is corroborated by statistical significance, but the Rh factor does not affect the outcome of the infection. Many studies report that blood type A might predispose to increased susceptibility of infection with SARS-CoV-2, and type O and Rh-negative blood groups might be protective. Although this appears to be an emerging trend, the impact of blood type on clinical outcomes remains ambiguous, since outcomes also largely depend on the capacities of healthcare systems. The possible limitations of our study were its observational approach and the relatively small number of patients. The size of the cohort is the sole reason for not being able to verify that the correlations we investigated do actually bear statistical significance, since analyses performed on small sample sizes require a greater margin of difference in order to conclusively and beyond doubt prove causality. This becomes most obvious in the segment of disease outcomes among Rh-positive and negative patients, where the numerical difference is absolute, but statistical assessment cannot confirm significance. Nevertheless, we do believe that the numerical observations are very obvious and consistent, justifying our conclusions and incentives. Further studies and more data, assessed on sizeable larger and representative population samples, are required in order to provide a generally applicable and definite proof to the thesis that there is a genuine connection between the ABO and Rh blood type on one side, and the susceptibility, severity and clinical outcome of the disease in patients with a COVID-19 infection on the other. Should such a correlation be confirmed with undisputable statistical significance, the observations should be used in shaping the system of preventive measures, as well as in guiding therapeutic procedures during possible future epidemic threats, with evolved strains of the same virus or with entirely new pathogens, if a similar relationship is investigated and eventually observed.

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Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Jun 14; 14(1):53-59.
https://doi.org/10.3889/oamjms.2026.12162
eISSN: 1857-9655
Category: *B – Clinical Sciences*
Section: *Surgery*

Divestment–Adventitia Resection in Order to Decrease Morbidity and Mortality and Improve R0/R1 Ratio in Curative Pancreatoduodenectomy for Advanced Pancreatic Head Carcinoma

Aleksandar Shumkovski[1]*, Ljubomir Ognjenovic[1], Robert Shumkovski[2], Arbijon Kolari[3]

[1]Clinic of Digestive Surgery, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia; [2]Clinic of Neurosurgery, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia; [3]Clinic for Surgical Diseases "St. Naum Ohridski", Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia

Citation: Shumkovski A, Ognjenovic Lj, Shumkovski R, Kolari A. Divestment–Adventitia Resection in Order to Decrease Morbidity and Mortality and Improve R0/R1 Ratio in Curative Pancreatoduodenectomy for Advanced Pancreatic Head Carcinoma. Open Access Maced J Med Sci. 2026 Jun 14; 14(1):53-59. https://doi.org/10.3889/oamjms.2026.12162
Keywords: Pancreatic head carcinoma; Pancreatoduodenectomy; Arterial divestment; Borderline resectable pancreatic cancer; R0 resection
***Correspondence:** Aleksandar Shumkovski. Clinic of Digestive Surgery, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia. E-mail: aleksum@yahoo.com
Received: 03-May-2026
Revised: 04-Jun-2026
Accepted: 12-Jun-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Pancreatic head carcinoma (PHC) is a highly aggressive malignancy associated with substantial morbidity, mortality, and poor long-term survival. Achieving an R0 resection margin during pancreatoduodenectomy (PD) is crucial for improving oncological outcomes. However, in borderline resectable (BRPHC) and locally advanced pancreatic head carcinoma (LAPHC), arterial involvement often necessitates complex arterial resections associated with high perioperative risks. Periarterial sub-adventitial divestment has emerged as a potential alternative to arterial resection, aiming to improve radicality while reducing complications.

AIM: To evaluate whether sub-adventitial arterial divestment during curative pancreatoduodenectomy decreases perioperative morbidity and mortality and improves the R0/R1 resection ratio in patients with BRPHC and LAPHC.

METHODS: A retrospective study was conducted on 50 consecutive patients with BRPHC or LAPHC treated between 2009 and 2017 following neoadjuvant therapy when indicated. All patients underwent extensive pancreatoduodenectomy with triangle operation, extended lymphadenectomy, and periarterial sub-adventitial divestment of the superior mesenteric, common hepatic, and/or celiac arteries. Clinicopathological data, perioperative morbidity, mortality, length of hospital stay, and R0/R1 resection status were analyzed.

RESULTS: Among the 50 patients, 27 (54%) were male and 23 (46%) were female, with a mean age of 63.1 ± 8.97 years. Overall mortality was 8% (4/50). Major complications included postoperative pancreatic fistula (24%), postoperative biliary fistula (2%), postpancreatectomy hemorrhage (4%), reoperation (6%), necrotizing pancreatitis (4%), thromboembolism (4%), cardiac failure (2%), and pulmonary complications (8%). Venous resection was required in 12% of patients. Postoperative pain relief was achieved in 92% of cases. Mean hospital stay was 10.56 ± 6.09 days. Histopathological examination demonstrated R0 resection in 28 patients (56%) and R1 resection in 22 patients (44%). Morbidity and mortality rates were comparable to standard PD and appeared lower than those reported for PD combined with arterial resection.

CONCLUSION: Sub-adventitial arterial divestment during pancreatoduodenectomy is a feasible and safe technique for selected patients with borderline resectable and locally advanced pancreatic head carcinoma. The procedure provides acceptable morbidity and mortality rates while achieving favorable R0 resection outcomes, representing a promising alternative to arterial resection in specialized high-volume centers.

Introduction

Pancreatic carcinoma is one of the most potential malignancies with high morbidity, mortality and poor prognosis concerning postoperative overall survival (OS) and postoperative disease-free survival (DFS). Incidence has risen in the last decades, affected by increase of the risk factors, from 9 to 12,2-13,6 per 100 000. It is now forth cause of death related to cancer in the west and sixth in the world [1], [2], [3]. In the meanwhile, the advance in surgical technique, procedures and devices for early precise screening, diagnosis and staging, also postoperative oncological treatment has not significantly improved the outcome after treatment of pancreatic carcinoma [4]. Morphological pattern is over 2/3 appearance on the head of the pancreas and 1/3 body and tail. The

diagnosis is often lately because of insidious and torpid clinical course at early stages. This particularly matters for pancreatic cancer of the body and tail. On the other hand, the pancreatic head carcinoma (PHC) appears to have more imminent clinical pattern and is likely to be diagnosed in the earlier stage, thus has generally better prognosis. This is still a controversial issue to be confirmed, though further prospective clinical trials are to be conducted [5], [6], [7].

Treatment of diagnosed PHC nowadays is a complex procedure consisting of neo adjuvant therapy (NAT), surgery and adjuvant therapy. NAT as a protocol varies among the centers, consisting of chemotherapy or chemo radio therapy. According to ISGPS, for resectable PHC the consensus is upfront surgery and then adjuvant therapy. On the other hand, for borderline resectable pancreatic (BRPHC) there is still unclear evidence of the predicted benefit. Though, after NAT radiologically can't be confirmed shrinkage or down staging. On the other hand, after NAT for BRPHC the studies expose lower rate of resections (lower resectability) but improvement in R0/R1 ratio, also OS after curative resections. Locally Advanced pancreatic head carcinoma (LA PHC) is determined by abutment of the arterial vessels (SMA, CHA, CT), and NAT is standard treatment, improving R0vR1 rate, also OS [8], [9], [10], [11]. Affecting this issue, hereby to mention, biopsy before NAT theoretically may cause seeding, and with radiation local desmoid inflammation which could cause worsening of the operative site. This could be the reason why majority of the surgeons prefer upfront surgery for resectable PHC, also BRPHC.

Standard surgical for PHC is pancreatoduodenectomy (PD), Whipple procedure. It is a complex and demanding procedure, which is to be performed in a high-volume tertiary center. The curative PD should provide R0 resection line, also certain number of lymph nodes to be retrieved. Recently there is a consensus reached by ISGPS for the extension of the procedure, either lymphadenectomy [12].

One of the most important goals for PD for PHC is R0, resection free margin. It is gross factor to determine future prognosis of the patient. In our series R0 was defined as minimum distance 1 mm of malignancy [13], [14], [15].

In certain cases, particularly in BRPHC or LAPHC achievement for R0 can be extremely difficult affecting the vascular abutment. For the veins is less demanding, skilled and trained surgeon is capable to resect and reconstruct the SMV or Portal Vein without excessive increase of the perioperative risk. PD with venous resection of the Portomesenteric trunc can be done safely without or with venous graft. The benefit of PD with venous resection compared to non-resected patients for OS is clear, but surprisingly, there is no difference in risk benefit with patients undergone PD without venous resection. More than that, there are studies reporting worst results in patients with venous resections compared with those without. This may be explained by the higher stage of the PHC at the time of resection, either worse biological malignant behavior of the tumor, or higher rate of R1 resection [16], [17], [18], [19], [20].

Speaking about arteries is quite another issue, the perioperative risk for morbidity and mortality is high, also postoperative quality of life (QOL) is poor. Present dilemma for arterial resection is the lack of benefit concerning the OS, also undesired rate of R0 resections, 65-75 % [21]. The most often arteries resected in this extensive PD are Celiac Trunk (CT), Superior Mesenteric Artery (SMA), Common Hepatic Artery (CHA). Concerning the disappointingly objective reality upon desired outcome, arterial resections during PD are not widely accepted. It should be done in high volume centers and in carefully selected patients, which can decrease perioperative morbidity, mortality and improve the OS. The assessment of the risk/benefit preoperatively and perioperatively should be done by angiography and peroperative dopler estimation of the arterial blood flow. The technique is meticulous microsurgery with obtaining sufficient blood flow [22], [23], [24], [25].

High morbidity and mortality with PD with arterial resection (PD AR), followed by unsatisfactory results in OS and DFS, encouraged the surgeons to find another way to obtain radicality-R0 resection margin, with decrease of the perioperative adverse events following arterial resection. Though, a delicate and meticulous procedure was invented by Nakao and Del Chiaro, divestment of the arteries with malignant abutment. Essentially, it is a complete resection of the adventitia of the arteries, altogether with the fat, fibrous, lymphatic and nervous tissue-peri arterial nervous plexus. This procedure provides additional layer and distance upon malignancy, reaching R0 in over 80 % of resections. Depicted procedure upon the arteries, resection or divestment, should be estimated preoperatively by the CICT, MRI, angiography, ai-PC estimation, finally intra operatively, meticulously defining the degree-layer of the malignant invasion to the arterial wall [21], [26], [27], [28]. So far recent studies suggest great options to use adventitia resection, meanwhile maintaining radical PD and reducing of perioperative morbidity and mortality imposed by arterial resection and reconstruction [29], [30]. In our opinion, not to defy the fact this procedure undoubtedly facilitates surgeon's effort either abbreviates operative time.

Primary end point of the study is to compare if there is decrease in perioperative morbidity and mortality for DP, and secondary end point, comparison of R0/R1 ratio to series with arterial resection.

Material and method

In our study from 2009 to 2017, we enrolled 50 consecutive patients with BRPHC, and LAPHC after

NAT. inclusion criteria for the population were radiologically resectable PHC, absence of liver metastases or peritoneal dissemination. All patients were preoperatively examined and staged with MRI, CICT, Ca19-9. For patients staged LAPHC, preoperatively was provided US guided or EUS biopsy and patients were referred and passed NAT.

Surgery was extensive Whipple procedure, PD, triangle operation. Pancreatic resection was not at the neck of the pancreas, but extended to the left, over the left margin of Superior Mesenteric Artery (SMA) (Figure 1).

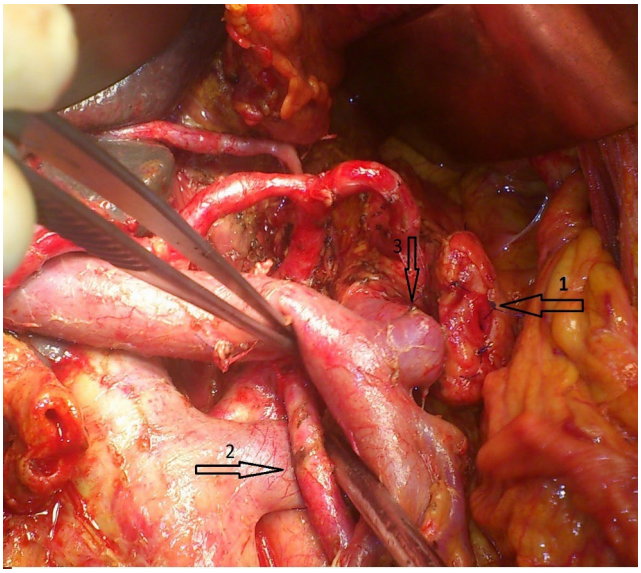

Figure 1: a) arrow 1: Pancreas respected to the left of SMA, over dissected Splenic Vein, b) arrow 2: dissected SMA; c) arrow 3: Splenic Vein

Procedure also contained hemigastrectomy, cholecystectomy followed with high resection of the common bile duct obtaining broad biliar resection margin.

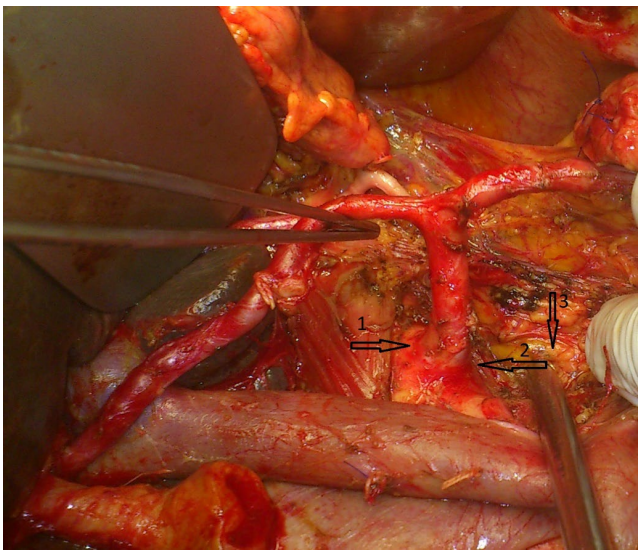

Figure 2: a) arrow 1: site of the resected right coeliac ganglion, b) arrow 2: site of resected left coeliac ganglion, c) arrow 3: suprarenal gland

Lymphadenectomy was also extended D3, beyond the consensus of the ISGPS, intended for staging with right renal hilys, interaortocaval dissection, 14th and 15th station also to the left surface of SMA, 11th station-Splenic Artery cleaning, 12th station-complete dissection of the hepatoduodenal ligament. Added procedure was bilateral Coeliac gangliectomy, at our opinion mitigating the adventitia resection-divestment of the CA, also pain relief (Figure 2).

The sub-adventitia resection-divestment was performed between the tunica adventitia (resected) and elastic lamina-tunica media of the artery. The procedure was delicate and meticulous, particularly to avoid lesion and consecutive post-traumatic pseudo aneurism of the artery.

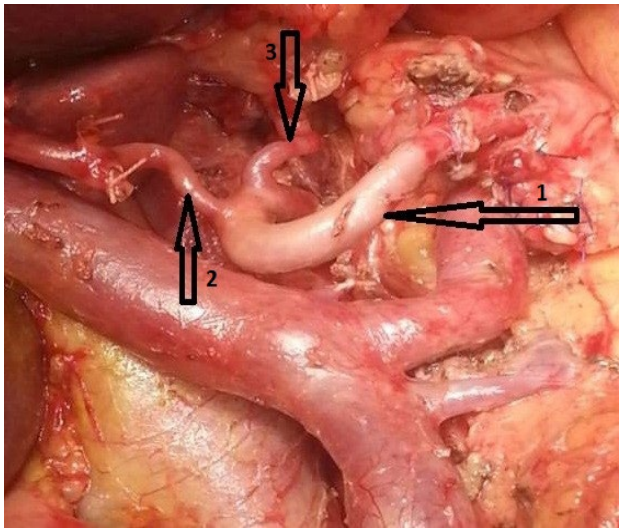

Figure 3: Subadvetitia resection, divestment of the arteries; a) arrow 1: Splenic artery, b) arrow 2: Hepatic artery, c) arrow 3: Right gastric artery, below CA

For SMA the procedure was completed en-block with the specimen altogether with the Uncinate process, and proceeded separately for CHA, CT (Figure 3, 4, 5).

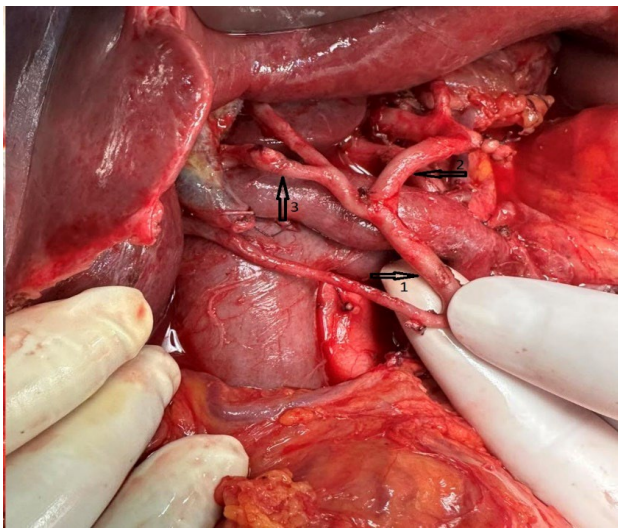

Figure 4: Subadvetitia resection, divestment of the arteries, anatomical arterial pattern with aberrant right hepatic artery; a) arrow 1: Right hepatic artery, b) arrow 2: Splenic artery; c) arrow 3: Left Hepatic artery

Reconstruction consisted of dunking T-L pancreatojejunostomy with interrupted sutures, T-L hepaticojejunostomy with interrupted sutures, retrocolic gastrojejunostomy, and jejunojejunostomy for exclusion of the omega loop.

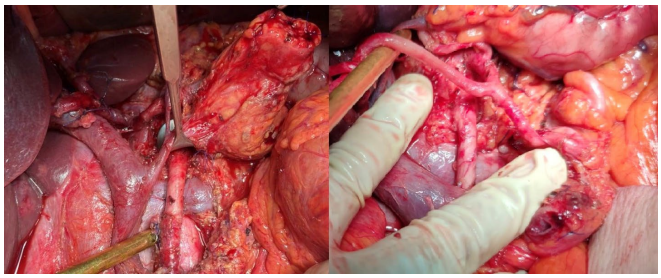

Figure 5: Subadvetitia resection, divestment of the arteries, SMA

Criterion for R0, free resection margin was ≥1 mm distance from the malignancy.

Results

In our group of 50, 27 patients were male (54 %), while 23 (46 %) were female. The age was 42 to 79, interval 63.10 ± 8.97.

Mortality rate in our study was 4 patients, 8%.

Morbidity was manifested in: 1. Postoperative Pancreatic Fistula (POPF); 2. Postoperative Biliar Fistula (POBF); 3. Perioperative blood loss/transfusion; 4. Postpancreatectomy hemorrhage (PPH); 5. Reoperation-revision; 6. Postoperative-post pancreatectomy necrotizing pancreatitis (PPNP); 7. Postoperative thromboembolism; 8. Cardiac failure insufficiency; 9. Pulmonary failure, pulmonary oedema, pleural effusion; 10. Added procedure-hemicolectomy, venous resections; and 11. Postoperative pain.

1. POPF: a) POPF B 9 patients, 18 %; b) POPF C 3 patients, 6 %.

2. POBF: 1 patient, 2 %.

3. Blood loss/Transfusion: a) 6 patients, 12 % received 350 ml, b) one patient, 2 %, received 700 ml transfusion;

4. PPH in 2 patients, 4 %.

5. reoperation-revision in 3 patients, 6 %.

6. PPNP suffered 2 patients, 4 %.

7. postoperative thromboembolism in 2 patients, 4 %,

8. cardiac failure-insufficiency with cardiac arrest in 1 patient, 2 %,

9. Pulmonary failure, pulmonary oedema, pleural effusion in 4 patients, 8 %.

10. Added procedure, a) in 2 patients, 4 %, right hemicolectomy was performed; b) 6 patients, 12 %, received portomesenteric venous resection, 3 with autologous graft from falciform hepatic ligament, 1 patient underwent resection of inferior vena cava (Figure 6, 7).

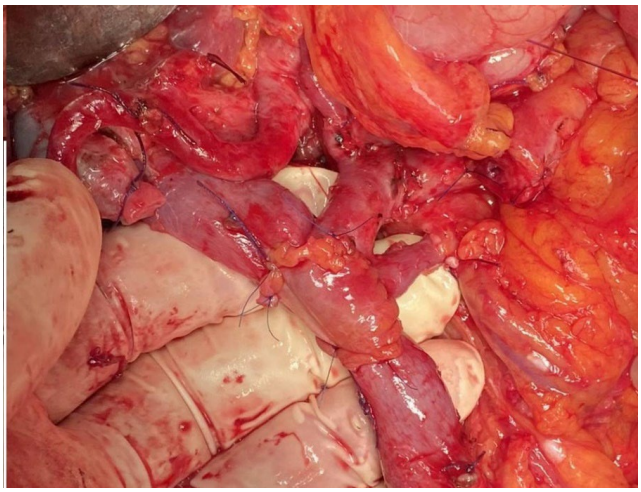

Figure 6: Resection of the portomesenteric vein with autologous free graft, falciform ligament

11. postoperative pain relief: in 4 patients 8% there was postoperative pain present, while 46, 92%, had pain relief.

Postoperative Intra hospital stay was from 8 to 31 postoperative days (POD). Average interval 10.56 ± 6.09.

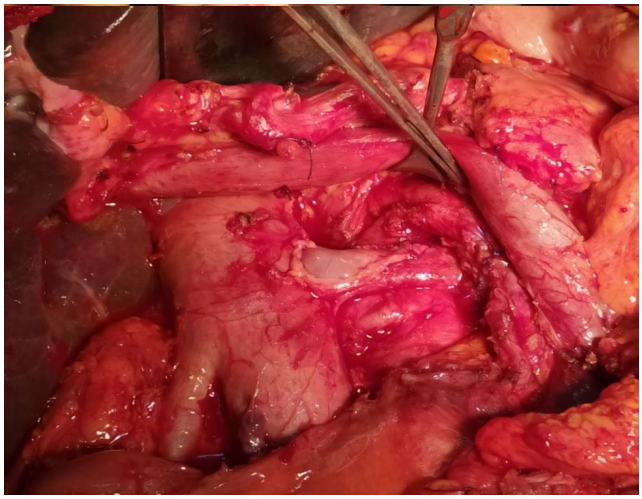

Figure 7: Resection of the Inferior vena cava, autologous free graft, falciform ligament.

R0/R1 was the second point. In our series we had 22 patients (44%), with R1 resection and 28 (56 %) with R0 resection margin.

Discussion

In our series morbidity was broadly dispersed affecting the clinical course and pattern. The most frequent complication was POPF, from total of 12, 9 patients (18%) suffered POPF B, which led to prolonged intra hospital stay, administration of antibiotic therapy, and parenteral hyper alimentation. There was no need for radiologically guided intervention, due to controlled fistula with by drain. The discharged volume of the drain gradually decreased, finally diminished, patients went well. This morbidity concerning POPF B in our patients with adventitia resection is in range to other series in high volume centers. The incidence, treatment, outcome are comparable and satisfactory [28], [29], [30], [31], [32], [33], [34], [35].

On the other hand, 3 of our patients suffered POPF C. They were all with prolonged hospital stay, re operated. The first one with POPF C was re operated, impair suture line was found, in the harsh operative environment subtotal pancreatectomy proceeded. The patient was discharged on the 31st POD. The second patient suffered simultaneously POPF C and POBF. The revision led to completion of pancreatectomy, and reconstruction of the biliodigestive anastomosis. Several days later patient developed sepsis, multi organ failure, leading to death. The last patient with POPF C was re operated on 8th POD, postoperative necrotizing pancreatitis was the background, leading also to PPH and lethal outcome [32], [33], [34], [35], [36], [37].

One patient suffered PPH devoid from another pathology, angiography was done, the source for bleeding couldn't be spotted. At the re reoperation, we didn't find the reason either, but postoperatively the patient had uneventful course, discharged in good condition.

Mortality in our series was 4 (8%). As mentioned before, 1 patient died from simultaneous POPF and POBF. The second reason for death was POPF C, postoperative necrotizing pancreatitis with PPH. The third and fourth lethal outcome were pulmonary thromboembolism and acute cardiac failure in patients with preoperative present risk factors, chronic myocardiopathy [37], [38], [39].

All these odds from our series we have analyzed are quite comparable superior to standard PD without adventitia resection-divestment. Since, when we match the results from our study with the results from centers and studies performing PD with arterial resection, we remain with another impression. Namely, morbidity is significantly higher than 30% [40]. Further studies with bigger number of patients observe also unsatisfying results, morbidity 54 %, mainly depending on POPF or PPH. In the same study, mortality was 13 %, grossly impacted by PPH [41].

One big systematic review and meta-analysis confirmed high morbidity, high mortality compared to divestment procedure. In this big study is also emphasized poor OS, thus barely justifying PD associated with arterial resections, particularly SMA [42].

The second end point of the study was R0/R1 ratio, particularly concerning it's high impact to OS. The pTNM findings among our patients confirmed 22 patients with R1 resection (44 %). This is barely satisfying but understandable while speaking for BRPHC and LAPHC. Several years earlier, when divestment began to be introduced, R1 resections we unacceptable high, some studies refer to over 80 %. In our early series the rate of R1 was also higher, and it decreased during the years by the enhance of the turnover [28], [29], [39], [43], [44]. The outcome for R0/R1 ratio in our series may appear better than reported results from some other high turnover centers, but it's necessary to mention we had lower number of patients with LAPHC after NAT than patients with BRPHC.

On the other hand, R0/R1 resection rate in PD with arterial resections remains high, generally unsatisfactory, particularly concerning morbidity, mortality and prognosis after arterial resections. According to some recent trials, total neo adjuvant therapy (TNT) may improve R0/R1 resections for BRPHC and LAPHC [45], [46].

Finally, in accordance with our opinion, it could be important to advance the radiological accuracy for preoperative distinction between BRPHC and LAPHC. This could precisely define the difference in R0/R1 ratio between BRPHC and LAPHC after adventitia resection-sub-adventitia divestment. More than that, it could enable accurate separate comparing of the R0/R1 ratio of both, BRPHC LAPHC after sub-arterial divestment to R0/R1 ratio after PD with arterial resection. Though, it may be particularly interesting to reveal the equity R0/R1 ratio after PD for LAPHC with sub-adventitia divestment to R0/R1 ratio after PD for LAPHC with arterial resection.

Conclusion

The sub-adventitia resection, divestment of the arteries for borderline resectable and locally advanced pancreatic head carcinoma so far delivered comparable improved result upon arterial resections. We consider the procedure safe, feasible, obtaining promising results concerning perioperative morbidity, mortality and R0/R1 ratio. Further broad adoption of the procedure by high volume centers may lead to desired avoidance of arterial resections.

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