Original article

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IMPACT OF IMFLAMMATION AND MALNUTRITION ON PRESSURE ULCER'S HEALING PROCES IN GERIATRIC PATIENTS- SINGLE CENTER EXPERIENCE FROM REPUBLIC OF NORTH MACEDONIA

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Inflammation is suggested to play an important role in the development of malnutrition in geriatric patients, but its association with pressure ulcers (PU) has been rarely studied. To examine the association of malnutrition and serum inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), with the healing of pressure ulcers among geriatric patients in long-term facilities. A total of 88 geriatric patients with PU were included in our study, additionally divided into two groups, moderate (n=45) and severe malnutrition (n=43). All patients received individualized nutritional support, including high-protein and blood products. We analyzed the PU healing process over 90 days and correlated it with four variables: serum albumin, hemoglobin, CRP, and ESR. The mean PUSH score decreased significantly over the 90-day follow-up period, from 10.89 ± 2.99 at baseline to 3.16 ± 2.73 at day 90 ($P < 0.01$). Elevated ESR and CRP levels demonstrated

a significant positive correlation with PU stage severity at all assessment time points (ESR: r = 0.33, P < 0.001; CRP: r = 0.57, P = < 0.001). Conversely, serum albumin and hemoglobin levels showed significant negative correlations with PU severity and PUSH scores (albumin: P = 0.000001; hemoglobin: P = 0.001503). This study provides evidence supporting the hypothesis that malnutrition-related systemic inflammation significantly contributes to PU healing and highlights the complex interplay between malnutrition and chronic inflammation. A reduction in inflammatory markers together with increases in serum albumin and hemoglobin was associated with better outcome and significant decline in PUSH score value.

Keywords: pressure ulcers, malnutrition, PUSH score, chronic inflammation

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UTICAJ UPALE I NEISHRANJENOSTI NA PROCES ZACELJIVANJA DEKUBUZA KOD GERIJATRIJSKIH PACIJENATA - ISKUSTVO JEDNOG CENTRA IZ REPUBLIKE SEVERNE MAKEDONIJE

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Pretpostavlja se da upala igra važnu ulogu u razvoju malnutricije kod gerijatrijskih pacijenata, ali je njena povezanost sa dekubitusima (engl. *pressure ulcer* – PU) retko proučavana. Cilj je bio ispitati povezanost malnutricije i serumskih inflamatornih markera, brzine sedimentacije eritrocita (SE) i C-reaktivnog proteina (CRP), sa zarastanjem dekubitusa kod gerijatrijskih pacijenata u ustanovama za dugotrajno lečenje. U našu studiju je uključeno ukupno 88 gerijatrijskih pacijenata sa PU, koji su dodatno podeljeni u dve grupe, umerenu (n=45) i tešku malnutriciju (n=43). Svi pacijenti su primali individualizovanu nutritivnu podršku, uključujući visok sadržaj proteina i krvnih proizvoda. Analizirali smo proces zarastanja PU tokom 90 dana i korelirali ga sa četiri varijable: serumskim albuminom, hemoglobinom, CRP i SE. Prosečan PUSH rezultat se značajno smanjio tokom perioda praćenja od 90 dana, sa 10,89 ± 2,99 na početku na 3,16 ± 2,73 na 90. dan ($P < 0,01$). Povišeni nivoi

sedimentacije eritrocita (SE) i SRP (CRP) pokazali su značajnu pozitivnu korelaciju sa težinom stadijuma PU u svim vremenskim tačkama procene (SE: r = 0,33, P < 0,001; CRP: r = 0,57, P = < 0,001). Nasuprot tome, nivoi serumskog albumina i hemoglobina pokazali su značajne negativne korelacije sa težinom PU i PUSH rezultatima (albumin: P = 0,000001; hemoglobin: P = 0,001503). Ova studija pruža dokaze koji podržavaju hipotezu da sistemska upala povezana sa malnutricijom značajno doprinosi zarastanju PU i ističe složenu interakciju između malnutricije i hronične upale. Smanjenje inflamatornih markera, zajedno sa povećanjem serumskog albumina i hemoglobina, bilo je povezano sa boljim ishodom i značajnim padom vrednosti PUSH rezultata.

Keywords: dekubiti, neuhranjenost, PUSH skor, hornična inflamacija

Introduction

Pressure ulcers (PU) and malnutrition are common conditions among residents of long-term care (LTC) facilities. According to the European Pressure Ulcer Advisory Panel (EPUAP), a PU is defined as a localized injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of pressure or a combination of pressure, shear, and/or friction (1). Epidemiological studies indicate an increased prevalence of PU among the geriatric population, up to 29% in LTC facilities, which is attributed to both intrinsic and extrinsic predisposing factors (2-5). Impaired nutritional status, together with physical immobility and cognitive impairments represent the most important intrinsic predisposing drivers for PUs in the elderly, whereas pressure, friction, shear, and incontinence act as main extrinsic factors contributing to PU development (2-3).

To provide a simple, time-efficient assessment of pressure ulcers and chronic wounds, the National Pressure Ulcer Advisory Panel developed the Pressure Ulcer Scale for Healing (PUSH) tool. This instrument is designed for routine use by physicians, nurses, and other healthcare professionals in both acute and long-term care settings. The PUSH tool enables standardized monitoring of wound healing over time by evaluating three key parameters: wound surface area (size), amount of exudate, and tissue type. Through systematic scoring of these components, clinicians can objectively track healing progress and assess the effectiveness of therapeutic interventions (6).

Although the association between nutrition and various chronic wounds is well documented, this association is rarely studied in PU (3, 7-10).

Malnutrition is highly prevalent in geriatric patients, with reported rates from 10% in independent old individuals up to two-thirds among the immobile elderly in LTC facilities (3-5). Aging itself is characterized by a chronic, low-grade inflammatory state, known as “inflammaging” (11). The extent to which inflammation in the elderly impacts nutrition remains unclear. Malnutrition in the elderly profoundly affects wound healing by modulating the inflammatory state. Together, malnutrition and inflammation form a vicious cycle, in which inadequate nutritional status impairs immunological defense mechanisms and promotes a pro-inflammatory state. Meanwhile, pro-inflammatory cytokines antagonize the appetite center in the central nervous system and promote muscle protein breakdown via the ubiquitin-proteasome pathway, thereby contributing to sarcopenia and frailty (11-12).

Inflammation is suggested to play an important role in the development of malnutrition, leading to anorexia, muscle catabolism, and metabolic changes (11). However, the exact relationship

between the degree of inflammation and the clinical response to nutritional support remains unclear, particularly in pressure ulcer research.

Considering the devastating effects of PUs on patients' well-being, the financial burden on healthcare systems, and the World Health Organization's prediction that children and adolescents will be outnumbered by the elderly by 2050, makes PUs one of the top priorities for modern medicine (11, 13).

Objectives

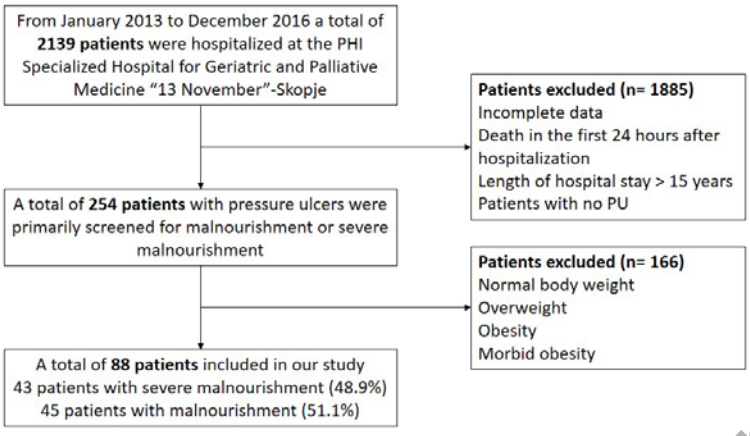
This study aimed to investigate the association between inflammatory markers—C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)—and malnutrition in geriatric patients with PUs residing in LTC facility. Furthermore, the study aimed to evaluate the impact of malnutrition severity on the healing process of stage I–IV PUs in malnourished and severely malnourished older adults.

Materials and methods

Study design

A prospective cohort study was conducted among 88 malnourished patients admitted to an LTC facility with PU; 43 (48.9%) were severely malnourished, while the remaining 45 (51.1%) were classified as malnourished. A flowchart of patient recruitment is presented in **Figure 1**. The patients were followed for 90 days to assess inflammatory markers (CRP and ESR), serum albumin and hemoglobin levels, and PU healing, using the Pressure Ulcer Scale for Healing (PUSH; 0=complete healing, 17=greatest severity) tool. Approval for conducting the research was obtained from the Institutional Review Board of Public Health Institution Specialized Hospital for Geriatric and Palliative Medicine "13 November**"-**Skopje, Republic of N. Macedonia. All patients received individualized nutritional support, including high-protein and blood products. Baseline and follow-up ulcer assessments (30^{th}, 60^{th}, and 90^{th} day) included ulcer measurement (length and width) and completion of the PUSH version 3.0 tool.

Figure 1. Flowchart of patient's recruitment in our study



Severity of malnutrition

Because of "anorexia of aging" and body composition changes (loss of muscle mass, increased fat), BMI cut-offs for older adults are generally higher than for younger populations (14).

The body mass index (BMI) was calculated as body weight divided by height squared (kg/m2). According to the Global Leadership Initiative on Malnutrition (GLIM) and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, malnutrition in patients ≥70 years is categorized as follow: Stage 1 (moderate malnutrition) required at least one phenotypic criterion: (1) 5%-10% weight loss within the past 6 months or 10%-20% from 6 months to 2 years; (2) low BMI corresponding to < 20 kg/m2 if < 70 years old, or < 22 kg/m2 if > 70 years old; (3) reduced muscle mass defined as CC < 33 cm for men and < 32 cm for women or mid-arm circumference < 21 cm. Stage 2 (severe malnutrition) required at least one phenotypic criterion: (1) > 10% weight loss within the past 6 months or > 20% beyond 6 months; (2) low BMI corresponding to < 18.5 kg/m2 if < 70 years or < 20 kg/m2 if > 70 years (15).

Main outcome measures

The primary endpoint was the change in the PUSH score. The secondary endpoint was a comparison of inflammatory markers (CRP and ESR) over 90 days. Additionally, we evaluated the correction of serum albumin and hemoglobin levels as biomarkers for the PUs healing process.

Statistical analysis

Data were analyzed using descriptive statistical methods. The total of 88 patients included in our study were divided into two groups (pathologically malnourished and malnourished). Categorical variables, including gender, age group, marital status, smoking status (smoker or non-smoker), and hospitalization stay, were summarized as absolute counts and percentages. We analyzed the pressure ulcer's healing process over the period of 90 days with correlation to four variables: serum albumins, hemoglobin levels, CRP and ESR.

Results

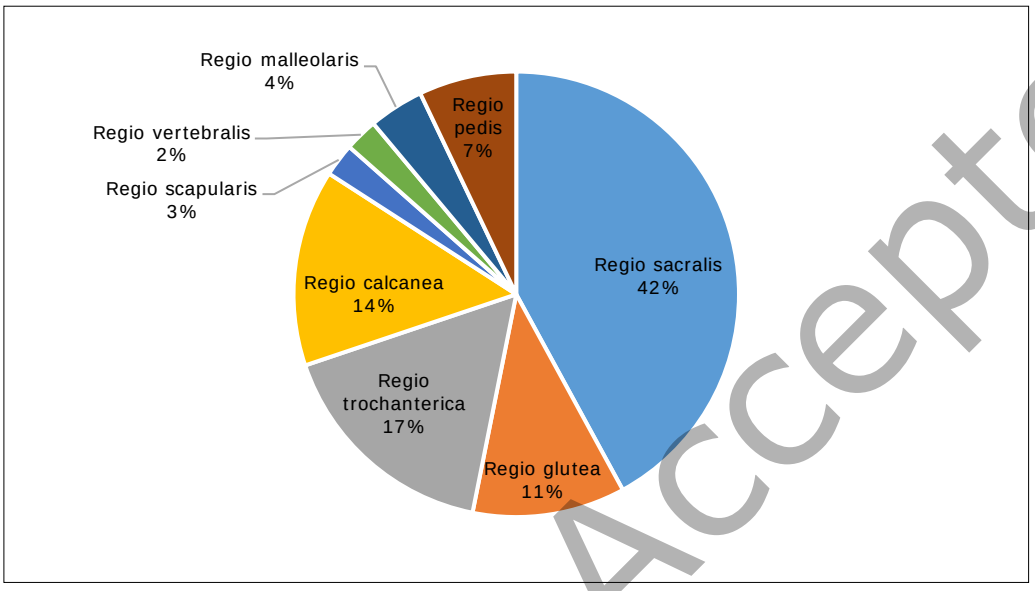
A total of 88 patients participated in the study, of whom 43 (48.9%) were diagnosed with pathological malnutrition and 45 (51.1%) with malnutrition. Of the examined sample, 40 patients (45.5%) were male, while the remaining 48 patients (54.4%) were female. The mean age of the patients was 76.6 ± 11.9 years, ranging from 38 to 95 years (see **Table 1**).

Table 1. Demographic, Clinical, and Laboratory Characteristics of the study population

	Malnutrition, BMI 45 (51.1%)	**Pathological malnutrition 43 (48.9%)**
Female, n (%)	21 (52.5%)	19 (47.5%)
Male, n (%)	24 (50.0%)	24 (50.0%)
Mean age (rang), SD, years	75.7 ± 12.0 38-95 years old	77.5 ± 11.9 38-93 years old
Total number of PU, n (%)	67 (53.2%)	59 (46.8%)
Mean PUSH score at the initial evaluation	**10.89 ± 3.06**	**10.95 ± 2.63**
Stage 1	/	/
Stage 2	19 (28.4%)	10 (16.9%)
Stage 3	36 (53.7%)	38 (64.4%)
Stage 4	11 (16.4%)	10 (16.9%)
Stage 5	1 (1.5%)	1 (1.7%)
Anatomical sites of PUs, n (%)		
Regio sacralis	28 (41.8%)	25 (42.4%)
Regio glutea	7 (10.4%)	7 (11.9%)
Regio trochanterica	11 (16.4%)	10 (16.9%)
Regio calcanea	9 (13.4%)	9 (15.3%)
Regio scapularis	1 (1.5%)	2 (3.4%)
Regio vertebralis	2 (3.0%)	1 (1.7%)
Regio malleolaris	3 (4.5%)	2 (3.4%)
Regio pedis	6 (9.0%)	3 (5.1%)

In our study, a total of 126 pressure ulcer locations were recorded, with the most frequent anatomical sites being the *regio sacralis* (42%), *regio trochanterica* (17%), and *regio calcanea* (14%) (see **Figure 2**).

Figure 2. Anatomical localization of PUs



One pressure ulcer was recorded in 58 patients (46.0%), two ulcers in 44 patients (34.9%), and three ulcers in 24 patients (19.1%). The total number of pressure ulcers in the study sample was 218 (see **Table 2**).

Table 2. Total number of pressure ulcers in the study population

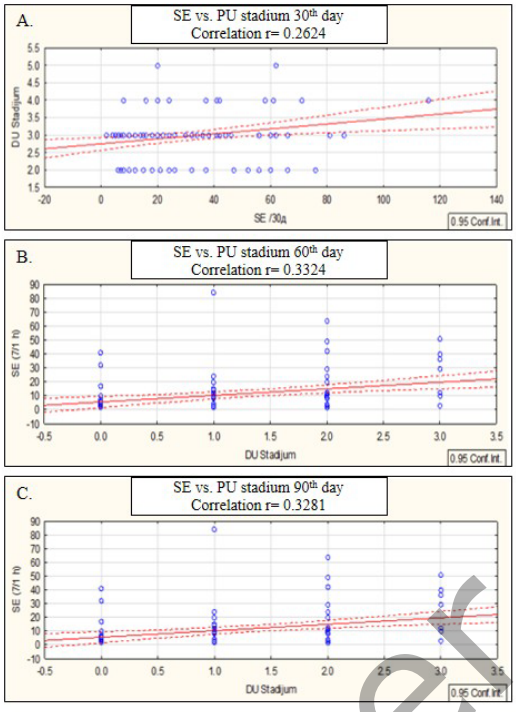
PUs number	***Count***	***%***
1	58	46.0
2	44	34.9
3	24	19.1
Total	126	100

A comprehensive panel of laboratory parameters was collected; however, the analysis primarily focused on evaluating the association between serum albumin, hemoglobin levels, the normalization of inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), and the healing dynamics of pressure ulcers over a 90-day observational period.

Our analysis showed that higher ESR values were associated with higher stage of pressure ulcers at all follow-up periods. Correlation analysis showed a statistically significant positive correlation between ESR values and the stage of pressure ulcers at day 30 ($r = 0.26$; $p = 0.003$), day 60 ($r = 0.33$; $p < 0.001$) and day 90 ($r = 0.33$; $p < 0.001$), indicating that increased

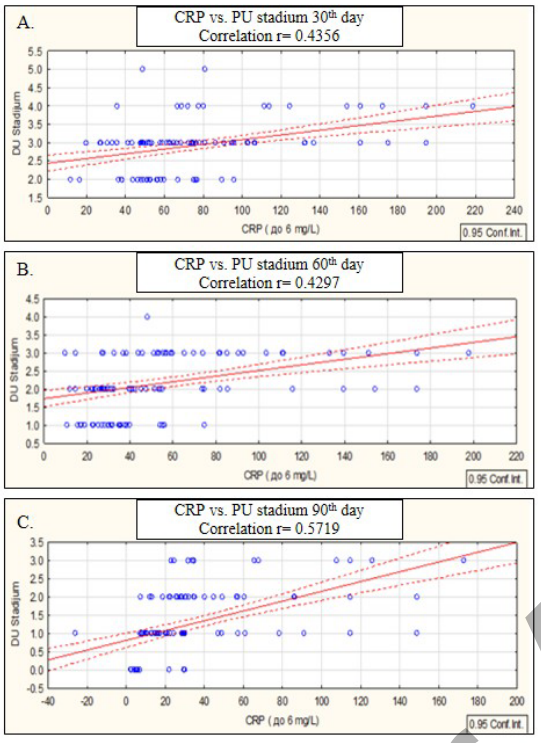
inflammatory activity is associated with more severe and slower healing ulcers (see **Figure 3 A, B, and C**).

Figure 3. Sedimentation rate and pressure ulcer stage at 30th (A), 60th (B), and 90th (C) day showing a positive moderate direct correlation



Correlation analysis showed a statistically significant positive and moderately strong correlation between CRP values and the stage of pressure ulcers at day 30 ($r = 0.44$; $p < 0.001$), day 60 ($r = 0.43$; $p < 0.001$) and day 90 ($r = 0.57$; $p < 0.001$). These results indicate that higher inflammatory burden is associated with more severe ulcers and slower healing (see **Figure 4 A, B, and C**).

Figure 4. CRP value and pressure ulcer stage at 30th (A), 60th (B), and 90th (C) day showing a significant positive moderately strong direct correlation



Serum albumin was significantly lower in patients with pathological malnutrition compared to patients with malnutrition at all-time points analyzed (see **Table 3**). In both groups, a gradual increase in serum albumin values was observed over time, with the Friedman ANOVA test showing statistically significant differences between the three time points ($p < 0.001$). This increase in albumin correlated temporally with an improvement in the clinical status of pressure ulcers.

Table 3. The average Albumin value in malnourished and severe malnourished patients

Albumins	***Average PM****	***Average M*****	***t-value***	***PM***	***M***	***SD PM***	***SD M***	***P value***
30th day	30.9	36.1	-5.16888	59	67	5.3614	5.9554	0.000001
60th day	33.2	38.4	-5.16888	59	67	5.3614	5.9554	0.000001
90th day	34.1	39.3	-5.16888	59	67	5.3614	5.9554	0.000001

PM* (pathologically malnourished patients); M** (malnourished patients)

Over the 90-day follow-up period a significant decrease in the mean PUSH score was observed, from 10.89 ± 2.99 at baseline to 3.16 ± 2.73 at day 90 ($P < 0.01$) (see **Figure 5**). A significant weak-to-moderate negative correlation was observed between albumin levels and PUSH

scores at both day 30 (p = 0.004) and day 90 (p = 0.010), indicating that higher albumin levels were associated with lower pressure ulcer severity over time (see **Figure 6**).

Figure 5. The average PUSH score in patients with malnutrition and pathological malnutrition on 30, 60, and 90 days observational period

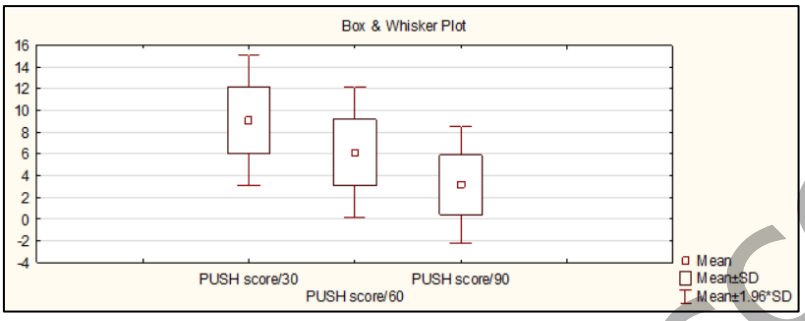
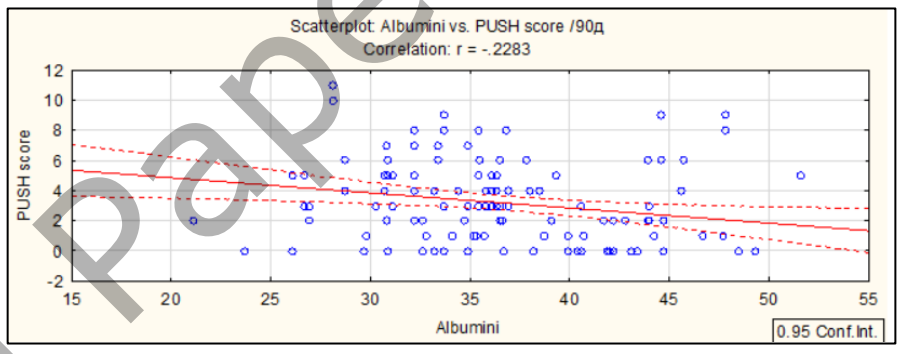


Figure 6. Correlation between albumin levels and PUSH score as an indicator for pressure ulcer's healing



The pathologically malnourished group exhibited significantly lower hemoglobin levels than the malnourished group of patients at all assessed time points (see **Table 4**). Despite a gradual increase in hemoglobin over time, values in the pathologically malnourished group remained consistently lower. Friedman ANOVA revealed statistically significant temporal changes in hemoglobin levels in both groups.

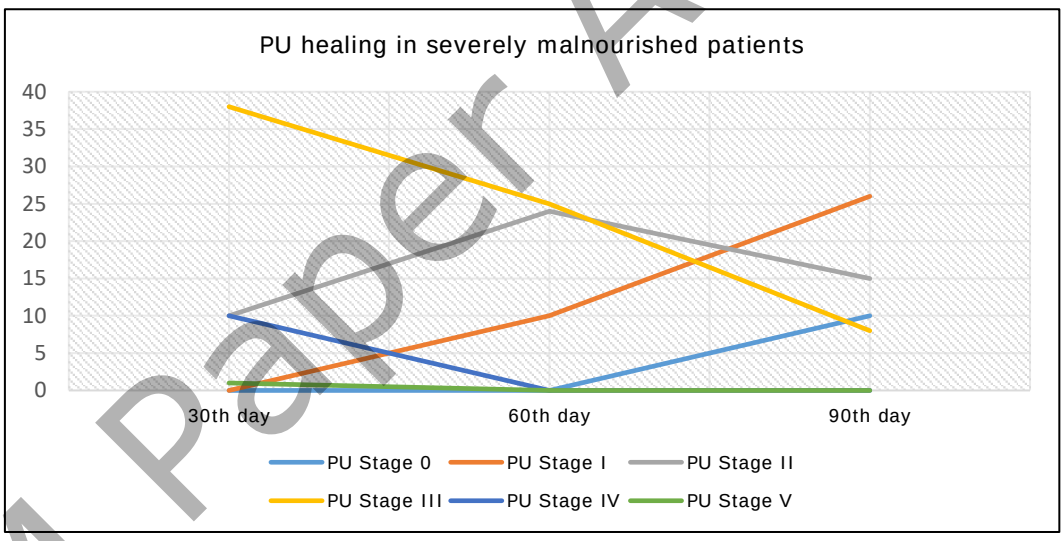
Table 4. The average Hgb value in malnourished and severe malnourished patients

Hgb	*Average PM**	*Average M***	*t-value*	*PM*	*M*	*SD PM*	*SD M*	*P value*
30th day	10.7	12.0	-3.24637	59	67	1.7871	2.7005	0.001503
60th day	12.2	13.5	-3.24637	59	67	1.7871	2.7005	0.001503
90th day	12.7	14.0	-3.24637	59	67	1.7871	2.7005	0.001503

PM* (pathologically malnourished patients); M** (malnourished patients)

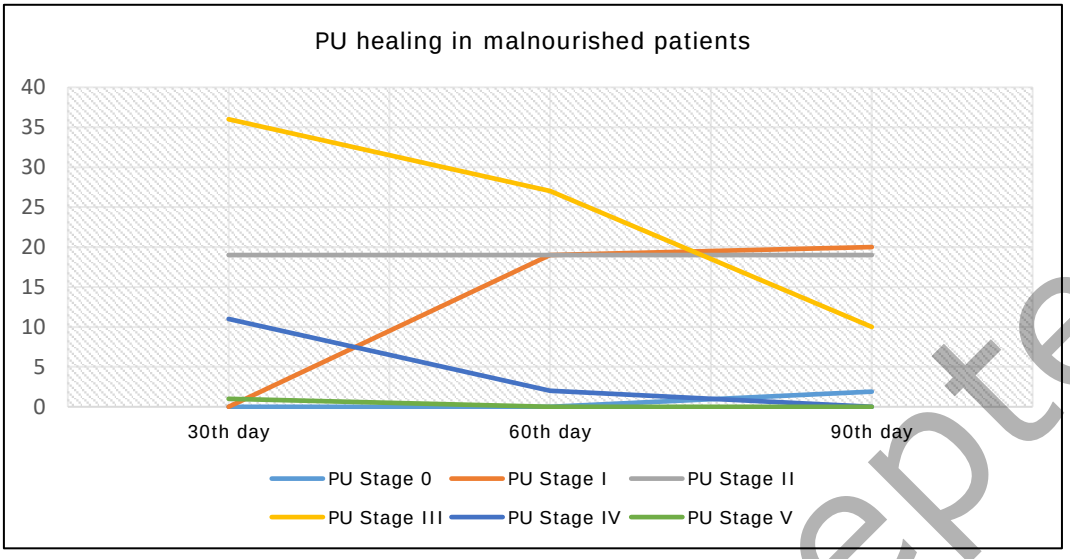
Over the 90-day follow-up, a progressive downstaging of pressure ulcers was observed in both groups. In the pathological malnutrition group, stages IV and V were no longer present by day 60, followed by a marked reduction in stage III (34.2%), increase in stage II lesions (37,5%) and stage I was registered for the first time (see **Figure 7**).

Figure 7. Dynamics of pressure ulcer's healing in severe malnourished patients over 90 days



Similarly, in the malnutrition group, stage IV lesions markedly declined by day 60 (81.8%), with continued reduction of stage III by 25% at day 60 and by 63% at day 90. Lower stages (I–II) remained stable or increased, and complete healing (stage 0) was first recorded at day 90 (see **Figure 8**). Overall, the dynamics index demonstrated a significant global reduction of higher-stage ulcers (III–IV) and a concurrent increase in lower stages and healed cases, indicating continuous wound improvement throughout the 90-day period.

Figure 8. Dynamics of pressure ulcer's healing in malnourished patients over 90 days



Discussion

PUs in geriatric patients represent challenging chronic wounds that are strongly associated with increased morbidity and mortality. Their development is closely linked to malnutrition, heightened susceptibility to infection, and impaired immune function (3-4). The substantial financial burden of PUs on healthcare systems, together with the global rise in life expectancy, underscores the need for comprehensive guidelines focused on prevention, early identification, and effective management of PUs (11). In 2007, EPUAP introduced a standardized definition and staging classification system for pressure ulcers (Stages I–IV), which was subsequently implemented in routine clinical practice in 2011 at the Public Health Institution Specialized Hospital for Geriatric and Palliative Medicine "13 November" – Skopje. In 2019 EPUAP introduced two additional stages of PU: unstageable pressure injury and deep tissue injury.

Wound healing is a complex process involving four consecutive stages: hemostasis, inflammation, proliferation, and tissue remodeling. On the molecular level, the skin restoration process is even more complex, with intertwined molecular pathways involving different cytokines, chemokines, and growth factors. In case when wound healing fails to restore the skin integrity, either pressure ulcer or other chronic wound arises. From molecular perspective, the newly published study by Lucía Tejero Peña et al. brought novel transcriptomic and proteomic biomarkers for pressure ulcers early detection into research focus. The transcriptomic profiling of patients with advanced stages of PUs (stage III-IV) uncover upregulation of *IER3, TSLP, CD177, DCSTAMP, C2CD4A,* and *TNFAIP6 gene*, and downregulation of *IL22RA1* and *IL17RD gene*. On the other hand, proteomic profiling identified decreased levels of IL-10, IFNγ, MCP-2/CCL8, and CXCL10. Finally, this study

introduces new insights into molecular explanation of immune dysregulaton and chronic inflammatory state in patients with PUs (16).

The close relationship between chronic inflammation and malnutrition in geriatric patients with PUs is well documented in studies to date (3, 7-10). The results of our observational study clearly add to thesis that nutritional and inflammatory status play a significant role in the healing dynamics of pressure ulcers. Serum albumin, hemoglobin levels, ESR, and CRP have been shown to be sensitive biomarkers of PU severity and healing rate.

Since 1974, serum albumin has been used as an indicator of nutritional status in severely ill patients. However, subsequent research has shown that in certain clinical scenarios—such as in patients with anorexia nervosa, those undergoing surgery or experiencing severe trauma, and even in overweight individuals—serum albumin levels may not reliably reflect nutritional status (17). Moreover, serum albumin levels are directly influenced by a variety of inflammatory cytokines, including IL-1β, IL-6, and TNF-α, which stimulate CRP production while simultaneously promoting albumin degradation and reducing its hepatic synthesis (2, 17). Albumin levels within ranges 35-50g/L are considered normal in our study. Our findings show that low albumin levels are associated with higher PU stages and slower healing, while a gradual increase in albumin over time parallels clinical improvement and a reduction in advanced stages. This suggests that serum albumin can be considered a prognostic marker for PU outcome. The results of this study are consistent with those of Sugino et al., who showed that higher serum albumin levels were associated with a greater likelihood of PU healing, confirming the role of albumin as a prognostic marker for ulcer outcome (17). Consistent with prior studies by Bourdel-Marchasson et al. (18) and Allman et al. (19), our results demonstrate that low serum albumin levels are closely linked to the number, severity, and healing of PUs (20). Current evidence suggests that serum albumin is a sensitive marker of active inflammation, with the lowest levels typically observed in patients with PUs and the highest CRP values. Maintaining albumin levels at ≥2.8 g/dL, combined with protein supplementation, has been linked to improved pressure ulcer healing (21). Similarly, Montalcini et al. found that low serum albumin (<3.1 g/dL) predicts the onset of PUs and is associated with higher mortality (22). Ultimately, low albumin levels are associated with decreased collagen production and fibroblast activity, delayed angiogenesis, and impaired perfusion in wounded tissue due to low osmotic pressure. Hypoalbuminemia and hypoproteinemia in general are furthermore worsened by exudate-related protein loss (3).

In our study population, anemia was present in 4.5% of patients among the recorded chronic diseases. Anemia in geriatric patients is a common and multifactorial condition, most commonly caused by iron deficiency, gastrointestinal blood loss, and chronic inflammatory diseases. Iron deficiency anemia, characterized by reduced hemoglobin levels, predominates in this population and represents one of the dependent variables analyzed in our study. Low hemoglobin concentrations (below 120 g/L in women and 130 g/L in men) impair oxygen delivery to tissues, leading to local hypoxia and delayed tissue repair in patients with pressure ulcers (23). In our study, hemoglobin levels between 120 and 180 g/L are considered normal. Similar to serum albumin, hemoglobin levels are inversely related to CRP. Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate increased hepcidin secretion—a key negative regulator of iron metabolism—thereby contributing to reduced hemoglobin levels in patients with pressure ulcers (12).

In addition to serum albumin and hemoglobin, the assessment of inflammatory markers—particularly C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)—are of substantial clinical importance. ESR is a sensitive but nonspecific marker of inflammation and may be elevated in a wide range of pathological and physiological conditions, not limited to patients with PUs. In the present study, ESR values of 0–20 mm/h for men and 0–30 mm/h for women were considered within the normal range, acknowledging that ESR levels are influenced by age and sex (24).

Similarly, CRP is a sensitive but nonspecific acute-phase protein, and values <6 mg/L were regarded as normal in our study population. Elevated ESR and CRP levels were predominantly observed in patients with advanced-stage PUs, reflecting the presence of an ongoing chronic inflammatory process. These findings are consistent with the results reported by G. Singh, whose retrospective observational study, among other patient groups, demonstrated elevated inflammatory marker levels in patients with skin lesions (24).

With appropriate treatment of PUs and improvement in nutritional status, a significant reduction in both inflammatory markers was observed in our cohort. Our results demonstrate a clear association between inflammatory marker levels and pressure ulcer healing, thereby corroborating the findings reported by D. Tang et al (25).

Conclusion

The results of this study confirm that serum albumin, ESR, and CRP are important biochemical markers associated with the healing of PUs. Lower albumin levels, together with elevated

sedimentation rate and CRP values, are associated with more advanced ulcer stages and slower clinical improvement, highlighting the detrimental effects of malnutrition and systemic inflammation on tissue regeneration.

A gradual increase in serum albumin, accompanied by a parallel decrease in inflammatory markers, correlates with reduced severity of decubital ulcers and progression to lower ulcer stages, including complete healing. These findings indicate that optimizing nutritional status and controlling the inflammatory response are essential components in the management of patients with decubital ulcers.

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