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Hamidiye Med J 2023;4(Suppl 1):1-8

Disease Diagnosis Distribution in Patients with Anemia and Elevated Sedimentation Above 50 mm/hr: A Single-center Experience

Anemi ve 50 mm/saat Üzerinde Sedimentasyon Yüksekliği Olan Hastalarda Hastalık Tanı Dağılımı: Tek-merkez Deneyim

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ABSTRACT

Background: Erythrocyte sedimentation rate (ESR) is a simple and inexpensive blood test with low sensitivity and specificity. However, it can be affected by many factors and there is no limit value valid for all patients. Anemia is also a phonemenon that should be investigated for many diseases. Sedimentation is a criterion in the diagnosis and follow-up of diseases in which both inflammation and autoimmunity are considered to be involved in the etiology, such as temporal arteritis and inflammatory bowel disease. A sedimentation rate of 50 mm/h or less is an exclusion criterion in vasculitis. In this study, we aimed to determine the distribution of disease diagnosis in patients with elevated sedimentation above 50 mm/h and anemia.

Materials and Methods: Ethics committee approval numbered B.30.2.PAÜ.0.20.05.09/187 was obtained for the study. The data of 300 patients with anemia and elevated sedimentation who were admitted to the Outpatient Clinic of Pamukkale University Hospital Internal Medicine and related subspecialties and who were hospitalized in the wards of Pamukkale University Hospital Internal Medicine and related subspecialties between November 2011 and November 2012 were retrospectively analyzed.

Results: A total of 300 patients with ESR exceeding 50 mm/h and anemia were identified. Of the patients, 154 were female (51.3%) and 146 were male (48.7%). The mean age of the women was 59.08±19.0 years and the mean age of the men was 62.4±14.1 years. The mean ESR was 77.55±21.21 mm/h in women and 82.89±19.24 mm/h in men. The mean hemoglobin was 10.31±1.60 g/dL in women and 10.69±1.52 g/dL in men. In the distribution according to disease groups, oncologic diseases had the highest rate (27.9%) and pulmonary diseases had the lowest rate (1%).

Conclusion: No difference was detected in the diagnostic distribution of the patients after lowering the lower limit of ESR to 50 mm/h compared to the literature. When the correlation between hemoglobin and ESR was examined, it was determined that ESR increased as hemoglobin decreased. We recommend differential diagnosis with further investigation especially in patients with high ESR accompanied by anemia.

Keywords: Anemia, cancer, erythrocyte sedimentation rate, inflammation, malignancy

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ÖZ

Amaç: Eritrosit sedimentasyon hızı (ESH) basit ve ucuz, ancak duyarlılığı ve özgünlüğü düşük bir kan testidir. Ancak birçok faktörden etkilenebilir ve herkes için geçerli bir sınır değeri yoktur. Anemi de birçok hastalık için araştırılması gereken bir bulgudur. Temporal arterit ve enflamatuvar bağırsak hastalığı gibi etiyolojisinde hem enflamasyonun hem de otoimmünitenin rol aldığı düşünülen hastalıkların tanı ve takibinde sedimentasyon bir kriterdir. Vaskülitlerde 50 mm/saat ve altında olması bir dışlanma kriteridir. Bu çalışmada 50 mm/saat üzerinde sedimentasyon yüksekliği ve anemisi olan hastalarda hastalık tanı dağılımını belirlemeyi planladık.

Gereç ve Yöntemler: Çalışma için B.30.2.PAÜ.0.20.05.09/187 sayılı etik kurul onayı alındı. Kasım 2011 ile Kasım 2012 arasında Pamukkale Üniversite Hastanesi İç Hastalıkları ve ilgili yan dallarının polikliniğine başvurmuş ve Pamukkale Üniversite Hastanesi İç Hastalıkları ve ilgili yan dallarının servislerinde yatırılarak takip edilen anemi ve sedimentasyon yüksekliği olan 300 hastanın verileri retrospektif incelendi.

Bulgular: ESH'si 50 mm/sa'yi geçen ve anemisi olan 300 hasta belirlendi. Hastaların 154'ü kadın (%51,3) 146'sı erkekti (%48,7). Kadınların yaş ortalaması 59,08±19,0 yıl, erkeklerin yaş ortalaması ise 62,4±14,1 yıl olarak tespit edildi. ESH kadınlarda ortalama 77,55±21,21 mm/sa, erkeklerde ise 82,89±19,24 mm/sa saptandı. Hemoglobin kadınlarda ortalama 10,31±1,60 g/dL, erkeklerde ise 10,69±1,52 g/dL saptandı. Hastalık gruplarına göre dağılımda en yüksek oranı onkolojik hastalıklar alırken (%27,9), en az hasta içeren grup ise göğüs hastalıkları (%1) olmuştur.

Sonuç: ESH alt sınırını 50 mm/sa'ye düşürmekle hastaların tanı dağılımında literatürle karşılaştırıldığında farklılık saptanmadı. Hemoglobin ile ESH arasındaki korelasyona bakıldığında hemoglobinin düştükçe ESH'nin arttığı saptandı. Özellikle yüksek ESH'ye aneminin eşlik ettiği hastalarda ileri tetkik ile ayırıcı tanının yapılmasını öneririz.

Anahtar Kelimeler: Anemi, kanser, eritrosit sedimentasyon hızı, enflamasyon, malignite

Introduction

The most valuable test in the determination of anemia is hemoglobin determination (1,2,3). According to the definition of the World Health Organization, anemia is defined as a hemoglobin level below 13 g/dL in men over the age of 15, 12 g/dL in women over the age of 15 who are not pregnant, and 11 g/dL in pregnant women (4).

The sedimentation rate is a diagnostic aid in many diseases. It is a blood test which is widely used, simple and results are obtained in a short time, but has low sensitivity and specificity (5,6,7,8). Erythrocyte sedimentation rate (ESR) displays a physiologic increase with age. It is measured higher in women than in men, in patients with hypercholesterolemia than in those without hypercholesterolemia and at low altitude than at high altitude (9,10). Commonly accepted reference values have been determined as 15 in men under the age of 50 years and 20 in women, 20 in men aged 50-85 years and 30 in women, and 30 in men over 85 years and 42 mm/h in women.

ESR is a helpful test for inflammatory, malignant and infectious diseases in the clinic and provides general information about body temperature, pulse and leukocyte count. In case of increased ESR, the patient's age, gender and medications should be taken into consideration.

ESR is one of the tests frequently utilized in the evaluation of acute phase response. Acute phase reaction includes events (inflammation, coagulation, complement activation, endothelial activation) characterized by the development of a number of simultaneous or successive reactions (inflammation, coagulation, complement activation, endothelial activation) with cytokines released from the responding cells (polymorph nucleated leukocytes, antigen presenting cells and endothelium) in the presence of a stimulus (11).

Stimuli (infection, trauma, immunologic/allergic reactions, surgical intervention, hypoxia, burn, malignancy) that lead to the development of an acute phase reaction cause tissue damage. Cytokine release occurs within 1-2 hours following the onset of inflammation, with the earliest response being neutrophilia and fever. Subsequently, serum iron and zinc levels decrease and the synthesis of some proteins in the liver is affected. When tissue damage occurs, especially serum fibrinogen, serum amyloid A protein and C-reactive protein (CRP) levels increase and albumin levels decrease. The increase in many asymmetric molecules such as fibrinogen and gammaglobulin accelerates erythrocyte aggregation. ESR increases. In our study, we evaluated the relationship between anemia and ESR.

Material and Methods

Ethics committee approval numbered B.30.2.PAÜ.0.20.05.09/187 was obtained for the study. The files of approximately 4.000 patients who were admitted to the Outpatient Clinics of Pamukkale University Hospital Internal Medicine and related subspecialties and who were hospitalized and followed up in the wards of Pamukkale University Hospital Internal Medicine and related subspecialties between November 2011 and November 2012 were retrospectively scanned in Probel HIS computer system. Those with ESR exceeding 50 mm/h and anemia were evaluated in accordance with the study criteria and

300 patients were included. If there was more than one ESR exceeding 50 mm/h during the measurements, the ESR with the highest value was recorded. The Hb level at the highest ESR value was recorded if it was below 13 g/dL in men and below 12 g/dL in women. Patients with ESR above 50 mm/h without anemia were excluded from the study. If there was more than one diagnosis, patients were enrolled in the most probable diagnostic groups that would increase ESR above 50 mm/h. The patient's age, gender, comorbidities, if any, medication use, ESR, hemoglobin level, bone marrow aspiration and biopsy, if any, and diagnosis were recorded.

Statistical Analysis

In the descriptive thesis, the data were evaluated in the SPSS 23.0 package program and the results were expresses as %, mean, and standard deviation. A p-value below 0.05 was considered significant.

Results

Of the 300 patients with anemia and ESR above 50 mm/h, 154 were female (51.3%) and 146 were male (48.7%) (Table 1). The mean age of the women was 59.08±19.0 years and the mean age of the men was 62.4±14.1 years. Demographic and laboratory findings of the patients are summarized in Tables 1, 2 and 3. Of the 300 patients, 130 (43.2%) had known chronic diseases while 170 (56.8%) had no known chronic disease. Of the 300 patients, 118 (39.3%) were taking medication while 182 (60.7%) were not. Fifty-one patients (17%) underwent bone marrow aspiration biopsy for further investigation and 22 patients (7.3%) had malign infiltration. According to the bone marrow infiltration of 22 patients, lymphoma in 10 patients, acute myeloblastic leukemia in 6 patients, acute lymphoblastic leukemia in 4 patients and Waldenström macroglobulinemia in 2 patients were diagnosed.

Table 1. Demographic information and comorbidities of patients

	Female	Male
Number of patients	154 (51.3%)	146 (48.7%)
Mean age	59.08±19.0 year	62.4±14.1 year
History of comorbidities		
• Diabetes mellitus type 2	24 (15%)	33 (22%)
• Hypertension	25 (16%)	24 (16%)
• Thyroid-related diseases	6 (3%)	1 (1%)
• Rheumatologic diseases	5 (3%)	Absent
• Coronary artery disease	5 (3%)	11 (7%)
• History of malignancy	3 (2%)	5 (3%)
• Congestive heart failure	2 (1%)	3 (2%)
• Inflammatory intestinal disease	Absent	2 (1%)
History of medication use	55 (35%)	63 (43%)

When age groups were analyzed, the highest number of patients were between the ages of 60-70 years (75 patients) and the lowest number of patients were between the ages of 15-30 years (19 patients). When ESR was compared between age groups, the highest ESR was found between the ages of 60-70 years. When the ESR of the patient group under 30 years of age was compared with the ESR of the patient groups aged 30-39, 40-49, 50-59, 60-69, 70-79 and 80-100 years, the ESR of the patients in the 40-49, 50-59, 60-69, 70-79 age groups was found to be significantly higher (p=0.01; 0.04; 0.04; 0.03). According to the diagnosis groups, the highest mean ESR value was observed in the oncologic patient group (Table 4).

In the distribution by disease groups, oncological diseases and malign hematological diseases had the highest proportion (27.9%), followed by infectious diseases (19.9%), nephrological diseases (13.3%), rheumatological diseases (10.6%), gastroenterological diseases (9.6%), cardiovascular diseases (7.3%), endocrinological diseases (2.7%), and benign hematological diseases (2.3%). The group with the least number of patients was pulmonary diseases (1%) (Figures 1, 2). 5% patients could not be included in any group. The highest ESR was 140 mm/h in a 21-year-old female patient with active ulcerative colitis. In males, the highest ESR of 140 mm/h was recorded in a 70-year-old patient with Waldenström Macroglobulinemia.

When the correlation between hemoglobin and ESR was examined, it was determined that ESR increased as hemoglobin decreased. Diagnosis groups were compared with each other in terms of ESR. ESR of malignancy patients was significantly higher than ESR of cardiology,

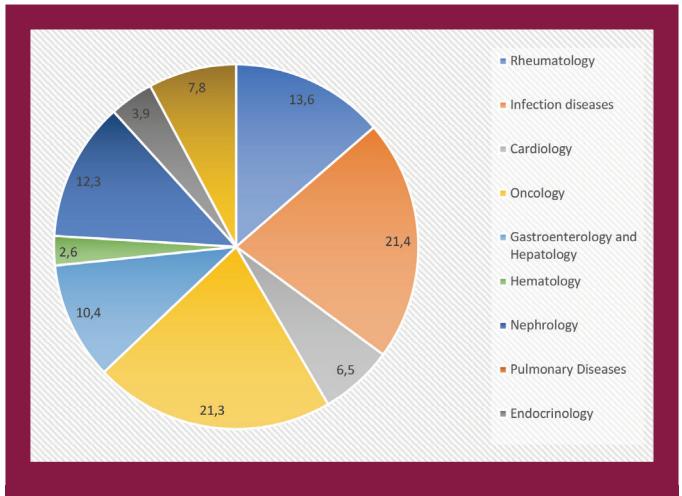

Figure 1. Distribution of patients by diagnostic group in females

gastroenterology and endocrinology patients (p=0.05; 0.01; 0.02).

We divided the patients into 4 groups according to anemia type. Patients diagnosed with hematologic malignancy were included in group 1, patients with iron deficiency anemia were included in group 2, patients with chronic disease anemia were included in group 3, and patients other than these anemias were included in group 4. The rates were 8.4% in group 1, 10.4% in group 2, 74.0% in group 3, and 7.1% in group 4 (Figure 3). In men, 6.2% in group 1, 7.5% in group 2, 84.2% in group 3, and 2.1% in group 4 (Figure 4).

Anemia types and ESR groups were compared and no significance was found between them (p=0.86). Albumin globulin ratio of 206 patients was analyzed. The number of female and male patients with an albumin globulin ratio below 1 was 34 and 49, respectively. There was a negative

Table 2. Biochemical and hematologic values of female patients included in the study

Laboratory data	Number of patients	Mean	Min	Max
White cell count (K/uL)	154	9.50±8.72	0,68	70,9
Neutrophil count (K/uL)	154	6.02±5.56	0,02	52,60
Lymphocyte count (K/uL)	154	2.23±3.99	0,29	40,09
Hb* (g/dL)	154	10.69±1.52	2,8	11,9
MCV* (%)	154	85.36±9.38	57	113
RDW* (%)	154	15.72±2.28	11,2	25
Ferritin (ng/mL)	94	339.65±502.43	2,4	2000
Vitamin B12 (pg/mL)	92	637.43±542.43	99,4	2000
Folic acid (ng/mL)	89	14.42±32.55	3,8	315
Albumin (g/dL)	147	3.44±0.65	2	5,2
Globulin (g/dL)	103	3.32±1	1,59	7,71
Albumin/globulin	103	1.11±0.37	0,16	2,36
C-reactive protein (mg/dL)	135	6.60±9.59	0,04	49
Blood urea nitrogen (mg/dL)	127	20.19±16.5	3	92
Creatinine (mg/dL)	145	1.13±1.21	0,29	6,3

*HB: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red cell distribution width

Table 3. Biochemical and hematologic values of the male patients included in the study

Laboratory data	Number of patients	Mean value	Min value	Max value
White cell count (K/uL)	146	9.40±5.68	0.58	49.8
Neutrophil count (K/uL)	146	6.45±4.09	0.10	29.2
Lymphocyte count (K/uL)	146	1.88±3.39	0.19	42.2
Hb* (g/dL)	146	10.31±1.60	5.1	12,9
MCV* (%)	146	85.36±9.38	59	117
RDW* (%)	146	15.72±2.28	11.7	30
Ferritin (ng/mL)	85	435±461.51	2.2	2341
Vitamin B12 (pg/mL)	92	581.01±506.78	44	2000
Folic acid (ng/mL)	85	12.94±30.82	3.3	286
Albumin (g/dL)	148	3.38±0.69	1.88	4.95
Globulin (g/dL)	103	3.35±1.35	1.02	11.9
Albumin/globulin	103	1.09±0.37	0.16	2.13
C-reactive protein (mg/dL)	142	7.70±8.12	0	38
Blood urea nitrogen (mg/dL)	141	25.82±21.85	2	112
Creatinine (mg/dL)	148	1.64±1.79	0.4	8.4

*HB: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red cell distribution width

correlation between albumin globulin ratio and ESR (Pearson correlation =-0.37 for women, Pearson correlation =-0.24 for men). There was a positive correlation between CRP and ESR (pearson correlation =0.19).

Discussion

Both ESR and hemoglobin values vary according to the age and gender of the patient (12). In the study of Aysalar et al. (13) including 500 patients, a very weak positive correlation was observed between age and ESR in all patients. It was found that ESR increased with a very weak correlation as age increased (r=0.186, p=0.0001). The correlation coefficient of this very weak relationship was r=0.182 (p=0.001) in women and r=0.170 (p=0.02) in men. A very weak correlation was determined between ESR and age in both genders (13). When ESR was evaluated according to age groups in our study, it was determined that ESR increased with increasing age in the ESR of the patient group up to the age of 70 years. ESR, which is expected to increase with increasing age, was determined to be lower in patients older than 70 years in our study compared to patients in the 15-69 age group.

Acceleration in ESR is more frequent in solid tumors than in hematologic malignancies. Lung, breast, colorectal and urinary system tumors are frequently associated with high ESR (14,15). In our study, the highest ESR was detected in the oncologic patient group and the lowest ESR was found in the pulmonology patient group.

Cengiz et al. (16) evaluated the distribution of disease diagnosis in 110 patients aged 65 years and older with ESR of 80 mm/h and above who were followed up in a geriatrics clinic. In the distribution by disease groups, infectious diseases had the highest proportion (48.2%) and oncologic diseases had the second highest proportion (17.3%). The most common infectious disease was

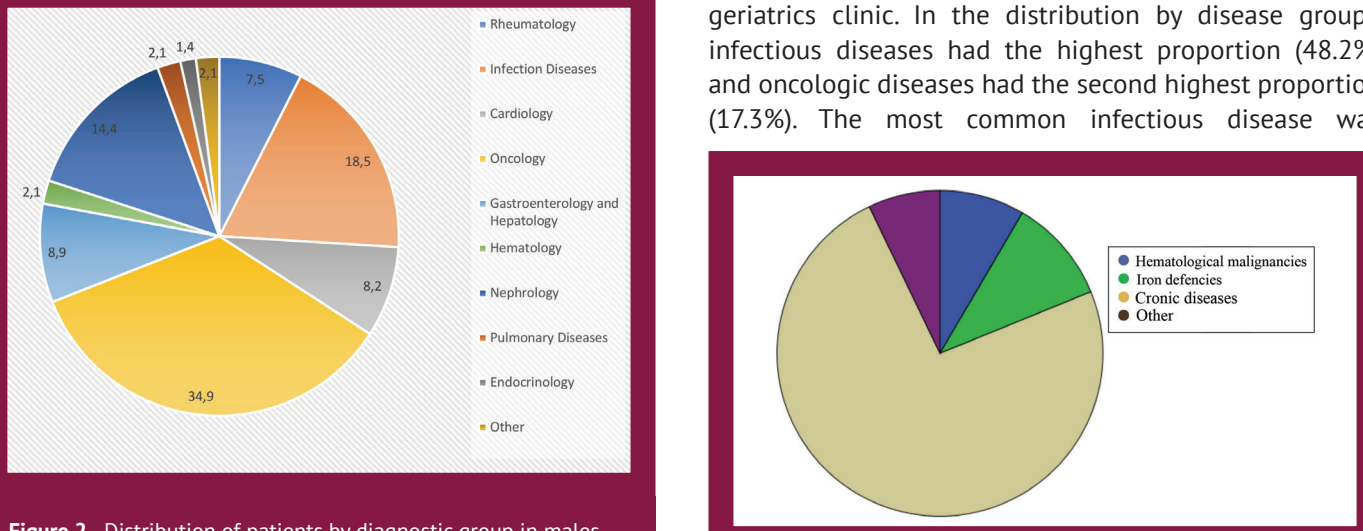

Figure 2. Distribution of patients by diagnostic group in males

Table 4. ESR according to diagnostic groups

	Mean value (mm/sa)	Min value (mm/sa)	Max value (mm/sa)
Rheumatic diseases	79.09±18.63	52	110
Infectious diseases	81.05±19.77	52	123
Cardiological diseases	72.55±18.07	52	116
Oncological diseases	86.46±21.40	52	140
Gastrointestinal and hepaticobiliary diseases	74.14±19.56	50	140
Hematologic diseases	69.57±21.18	52	115
Nephrological diseases	81.42±20.68	52	120
Pulmonary diseases	75.0±14.73	59	88
Endocrinologic diseases	72.25±19.6	53	99

Figure 3. Distribution of patients according to anemia type in females

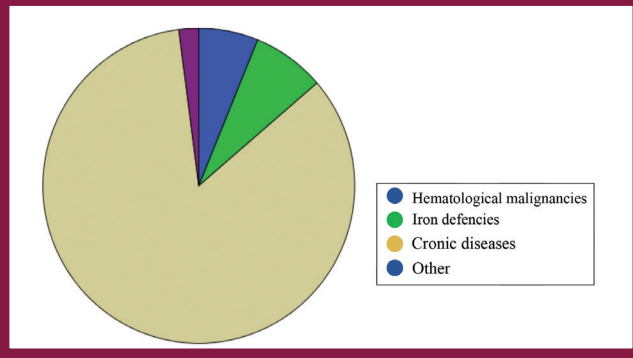

Figure 4. Distribution of patients according to anemia type in males

pneumonia with 37.7%. The most common malignancy was multiple myeloma with 32%. In our study, 16% of the patients had hypertension, 1.3% had coronary artery disease, 15% had type 2 diabetes mellitus and 56.8% had no known history of chronic diseases.

Haque et al. (17) evaluated 100 patients with ESR above 100 mm/h. The most common complaints of the patients were high fever, general malaise and pallor. While hematologic oncologic diseases were found in 41%, infectious diseases were detected in 36%. In our study, the most common complaint of the patients was fatigue with a rate of 30%.

Lluberas-Acosta and Schumacher (12) detected infection in 43, malignancy in 16, rheumatologic disease in 30, inflammatory disease in 7, renal dysfunction in 25 and diseases from different systems in 38 of 162 hospitalized patients with elevated ESR. Similarly, in a study conducted in Zimbabwe, infection was observed in 46, malignancy in 25, connective tissue disease in 17, kidney disease in 8 and liver disease in 5 of 101 patients with high ESR. In this study, pneumonia was found to be the most common infectious cause of elevated ESR, while multiple myeloma was the most common malignancy with the highest ESR (18). In our study, the highest ESR was found in patients diagnosed with ulcerative colitis and Waldenström Macroglobulinemia.

Kocabaş (19) of the 361 patients diagnosed with ESR above 100 mm/h, 41 (10.65%) had hematologic diseases and 146 (37.92%) had neoplastic diseases (including hematologic). Infectious diseases were detected in 172 (44.68%) patients, musculoskeletal and connective tissue diseases in 34 (8.83%) patients, chronic renal failure in 40 (10.39%) patients.

Baicus et al. (20), in a study conducted in Romania, determined that the likelihood of cancer increased with age in the presence of high ESR (>29 mm/h) and anemia; the positive predictive value was 64% and the negative predictive value was 91% in the presence of advanced age (>65), anemia and high ESR; neither age nor ESR nor anemia could rule out cancer, but they could increase the likelihood of cancer from 24% to 64% or decrease it from 24% to 9%.

Arvidson et al. (21) reported no correlation between daily activity score and ESR in patients with rheumatoid arthritis, but determined that CRP and fibrinogen levels were closely related and that fibrinogen determination would be more accurate than ESR in determining disease activity.

Bridgen (8) stated that ESR is still very useful when used meticulously; ESR above 100 mm/h is sufficiently sensitive, specific and significant and is related to a serious underlying disease with a 90% probability; in the presence of an extremely high ESR in an asymptomatic person, a conclusion can usually be reached with a few simple tests; if not, the test should be repeated after waiting a few months before starting very detailed and expensive examinations; and the use of ESR as a screening test would not be appropriate (22). In our study, ESR was detected to be 100 mm/h or above in 17.5% of women and 23.9% of men. Malignancy was detected in 48.1% and infection in 14.8% of 27 female patients with ESR ⩾100 mm/h. Among 35 male patients with ESR ⩾100 mm/h, 31.4% had malignancy and 28.5% had infection (23).

In vasculitis, a sedimentation rate of 50 mm/hour and below is an exclusion criterion (24). When the literature was reviewed, the lower limit value of ESR was determined as 100 mm/h in studies to determine the diagnostic distribution in patients with high ESR. In our study, the lower limit value of ESR was set as 50 mm/h, aiming to reach a wider patient group. Asymptomatic patients with anemia in addition to elevated ESR were included to exclude asymptomatic, unexplained patients with elevated ESR but followed up healthy patients. When compared with the literature, similar disease distributions were obtained. In the study by Sarı et al. (23) differently, in the distribution according to disease groups with ESR exceeding 100 mm/h, rheumatic diseases had the highest rate (30%) and cardiovascular diseases had the lowest rate (3%).

Baicus et al. (20) examined age, ESR and anemia values in 431 patients with weight loss. Cancer was diagnosed in 24% of the patients with further investigation. They recommended that patients with complaints of weight loss should be evaluated together with age, ESR and anemia and demonstrated the necessity of further examination in terms of cancer.

ESR is a diagnostic criterion in giant cell arteritis and polymyalgia rheumatica diseases and is always elevated in patients with giant cell arteritis, frequently above 90 mm/h (25,26). In our study, 1 patient was diagnosed with Polymyalgia Rheumatica and ESR was measured as 90 mm/h.

Gamaldo et al. (27) prospectively evaluated 827 patients aged 50-96 years with neurologic diseases such as cerebrovascular disease intermittently. High MCV levels were associated with significantly lower global mental status, long delayed memory and attention. Since the surface to volume ratio is small in macrocytic cells, erythrocytes collapse rapidly. In our study, a negative correlation was detected between hemoglobin and ESR. Anemia with elevated ESR was mostly a laboratory finding and was generally considered as an indicator of an underlying chronic disease.

Conclusion

ESR, especially excessive elevation is associated with many diseases, especially malignant diseases, infections and collagen tissue diseases. No difference was found in the diagnostic distribution of the patients after lowering the lower limit of ESR to 50 mm/h compared to the literature.

In our study, patients with ESR above 50 mm/h and anemia were included to exclude these patients. It was detected that anemia deepened as ESR increased. It was observed that ESR elevation was mostly accompanied by anemia of chronic disease. This indicates that anemia is a finding secondary to the disease causing ESR elevation.

ESR is a test with low specificity and sensitivity, although it is easy and inexpensive with quick results. Although it can still be useful in the provision of primary health care services in the diagnosis and follow-up of various diseases, it can lead to the performance of highly invasive tests, most of which are normal at high values. In this context, it is recommended that ESR is definitely not a screening test and in case of high values detected in asymptomatic individuals, after a detailed history and physical examination, it is recommended to proceed to further investigations starting with simple tests in patients who are still suspicious and who have anemia.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from Pamukkale University, numbered B.30.2.PAÜ.0.20.05.09/187.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: T.E.Ö., A.K., C.Ö., İ.S., S.H., İ.G., Concept: T.E.Ö., A.K., Design: T.E.Ö., A.K., C.Ö., İ.S., S.H., Data Collection or Processing: T.E.Ö., Analysis or Interpretation: T.E.Ö., C.Ö., İ.S., S.H., Literature Search: T.E.Ö., C.Ö., İ.S., S.H., İ.G., Writing: T.E.Ö., C.Ö., İ.S., S.H., İ.G.

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References

1. Atamer T, eds. İç Hastalıkları Bölüm 9 Kan Hastalıkları. İstanbul: 2005:597-645. [Crossref]
2. Atamer T. Anemilerin sınıflandırılması ve anemik hastaya yaklaşım. Klinik Hematoloji. İstanbul: Nobel Tıp Kitapevleri; 2003:33-45. [Crossref]
3. Waters HM, Seal LH. A systemic approach to the assesment of erythropoiesis. Clin Lab Haematol. 2001;23:271-283. [Crossref]
4. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. Geneva, World Health Organization, 2001 (WHO/NHD/01.3). [Crossref]
5. Reinhart WH. Erythrocyte sedimentation rate-More than an old fashion? Ther Umsch. 2006;63:108-119. [Crossref]
6. Piva E, Sanzari MC, Servidio G, Plebani M. Length of sedimentation reaction in undiluted blood (erythrocyte sedimentation rate): variations with sex and age and reference limits. Clin Chem Lab Med. 2001;39:451-454. [Crossref]
7. Saadeh C. The erythrocyte sedimentation rate: old and new clinical applications. South Med J. 1998;91:220-224. [Crossref]
8. Bridgen M. The erythrocyte sedimentation rate. Still a helpful test when used judiciously. Postgrad Med. 1998;103:272-275. [Crossref]
9. Choi JW, Pai SH. Influences of hypercholesterolemia on red cell indices and erythrocyte sedimentation rate in elderly persons. Clin Chim Acta. 2004;341:117-121. [Crossref]
10. Miao G. Reference values of erythrocyte sedimentation rate of adult healthy subjects. Arch Med Res. 2002;33:506-509. [Crossref]
11. Lewis SM, Bain BJ, Bates I, Dacie JV. Dacie and Lewis Practical Haematology. 9th ed. London: Churchill Livingstone; 2001:527-543. [Crossref]
12. Lluberas-Acosta G, Schumacher HR Jr. Markedly elevated erythrocyte sedimentation rates: consideration of clinical implications in a hospital population. Br J Clin Pract. 1996;50:138-142. [Crossref]
13. Aysalar U, Sandıkçı S, Akpınar E, Saatçi E. Erythrocyte Sedimentation Rate And C-Reactive Protein: Are They Still Worthwhile? Türk Aile Hek Derg. 2007;11:154-162. [Crossref]
14. Koçar IH, Erikçi S, Ünübol S. Eritrosit sedimentasyon hızı ve klinik değeri. Türkiye Klinikleri J Med Sci. 1989;9:174-181. [Crossref]
15. Shearn MA, Kang IY. Effect of age and sex on eythrocyte sedimentation rate. J Rheumatol. 1986;13:297-298. [Crossref]
16. Cengiz OK, Esmen SE, Varli M, Yalcin A, Aras S, Atmis V, et al. Markedly elevated erythrocyte sedimentation rate in older adults. How significant clinically? Eur Geriatr Med. 2013;4:28-31. [Crossref]
17. Haque Z, Jakiul A, Mesbahuddin N. Clinical study on patients with grossly elevated erythrocyte sedimentation rate. J Med 2007;8:64-68. [Crossref]
18. Stein CM, Xavier R. Extreme elevation of the erythrocyte sedimentation rate in patients admitted to a general medical ward in Harare, Zimbabwe. J Trop Med Hyg. 1989;92:259-262. [Crossref]
19. Kocabaş C. Erişkin yaş grubunda 100 mm/h ve üzeri eritrosit sedimentasyon hızının nedenleri (Tıpta Uzmanlık Tezi). İzmir: Dokuz Eylül Ünivesitesi; 1995. [Crossref]
20. Baicus C, Ionescu R, Tanasescu C. Does this patient have cancer? The assessment of age, anemia, and erythrocyte sedimentation rate in cancer as a cause of weight loss. A retrospective study based on a secondary care university hospital in Romania. Eur J Intern Med. 2006;17:28-31. [Crossref]
21. Arvidson NG, Larsson A, Larsen A. Disease activity in rheumatoid arthritis: Fibrinogen is superior to the erythrocyte sedimentation rate. Scand J Clin Lab Invest. 2002;62:315-319. [Crossref]
22. Brigden ML. Clinical utility of the erythrocyte sedimentation rate. Am Fam Physician. 1999;60:1443-1450. [Crossref]
23. Sarı O, Sağlam K, Tanoğlu A, Korucu AR, Bulucu F, Erikçi S. A retrospective analysis of diseases with an erythrocyte sedimentation rate exceeding 100 mm per hour. Gulhane Med J. 2007;49:163-167. [Crossref]
24. Burns JC, Mason WH, Glode MP, Shulman ST, Melish ME, Meissner C, et al. Clinical and epidemiologic characteristics of patients referred for evaluation of possible Kawasaki disease. United States Multicenter Kawasaki Disease Study Group. J Pediatr. 1991;118:680-686. [Crossref]

25. Ontario Association of Medical Laboratories. Guideline for the ordering of erythrocyte sedimentation rate (ESR). Revised 2001. [Guidelines for clinical laboratory practice]. Retrieved June 26, 2006. [Crossref]
26. Berlit P. Clinical and laboratory findings with giant cell arteritis. J Neurol Sci. 1992;111:1-12. [Crossref]
27. Gamaldo AA, Ferrucci L, Rifkind J, Longo DL, Zonderman AB. Relationship between mean corpuscular volume and cognitive performance in older adults. J Am Geriatr Soc. 2013;61:84-89. [Crossref]

ORIGINAL ARTICLE

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Examination of the Quality of Life and Physical Fitness Status of Healthcare Students in the Post-pandemic Process

Pandemi Sonrası Süreçte Sağlık Hizmetleri Öğrencilerinin Yaşam Kalitesi ve Fiziksel Uygunluk Durumlarının İncelenmesi

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ABSTRACT

Background: Measures taken during the coronavirus pandemic and remote implementation of education have led young people to spend less time on physical activity and become sedentary. This situation not only contributes to an increase in fat mass and therefore an increase in body mass index, and the early onset of various non-communicable chronic diseases but also poses a threat to the physical fitness of healthy young people. Furthermore, all of these negative effects significantly affect the quality of life. During the period when a gradual exit from pandemic conditions is taking place and face-to-face education has started, the aim was to determine the physical fitness and quality of life perceptions of adult young people by collecting physiological and health-related quality of life data and to evaluate them from a physiological perspective by identifying the possible link between these fundamental parameters, if any.

Materials and Methods: The data of a total of n=213 students from 7 different programs attending İstanbul University-Cerrahpaşa, Vocational School of Health Services in the 2021-2022 academic year were collected using a survey method.

Results: When we look at the ratio of participants, it was observed that daily step count, which is one of the indicators of physical fitness, was higher in males than females, but there was no significant difference. General health perception scores were low at 38.37 points. The value of the general change perception in health over the past year was also determined to be 55.94 points.

Conclusion: With this study, it has been concluded that it is not a safe approach to directly correlate daily step count with physical fitness alone and that more precise judgments can be reached by adding different parameters such as heart rate and calorie expenditure, instead of just accepting 9.500 daily steps as a clear indicator of physical fitness. It also suggests that studies to be conducted in the coming years to correlate participants' quality of life perceptions with their physical fitness should be supported.

Keywords: Physical fitness, quality of life, pandemic, health parameters

ÖZ

Amaç: Koronavirüs pandemisi sürecinde uygulanan önlemler ve eğitimin uzaktan gerçekleştirilmesi, gençlerin fiziksel aktiviteye daha az zaman ayırmasına ve hareketsiz (sedanter) hale gelmesine neden olmuştur. Bu durum, yağ kitlesinin artışına, dolayısıyla vücut kitle indeksinin artışına ve çeşitli bulaşıcı olmayan kronik hastalıkların erken başlamasına katkıda bulunabileceği gibi sağlıklı gençlerin fiziksel uygunluğuna karşı bir tehdit de oluşturmaktadır. Dahası, tüm bu olumsuz etkiler yaşam kalitesini önemli ölçüde etkilemektedir. Pandemi koşullarından kademeli bir çıkışın gerçekleştiği ve yüz yüze eğitimin başladığı dönemde erişkin gençlerin gerek fizyolojik gerekse sağlıkla ilişkili yaşam kalitesi verilerini toplayarak onların fiziksel uygunluğu ve yaşam kalite algılarını belirlemesi, eğer var ise bu temel parametreler arasındaki bağlantıyı tespit ederek fizyolojik bir bakış açısı ile değerlendirmesi amaçlandı.

Gereç ve Yöntemler: Çalışmada 2021-2022 eğitim öğretim yılında eğitimine başlayan İstanbul Üniversitesi-Cerrahpaşa, Sağlık Hizmetleri Meslek Yüksekokulu'nda eğitim gören 7 ayrı programdan toplam n=213 öğrencinin verileri anket yöntemi ile toplandı.

Bulgular: Katılımcıların oranına baktığımızda 64 adet erkek, 149 adet kadın öğrencinin verileri değerlendirildiğinde fiziksel uygunluğun göstergelerinden biri olarak kabul edilen günlük adım sayısının erkeklerde kadınlara oranla daha yüksek olduğu ancak

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ÖZ

anlamlı bir farklılığın oluşmadığı gözlendi. Genel sağlık algısı puanlarının 38,37 gibi düşük bir puanda kaldığı görüldü. Son bir yılda sağlıkta olan genel değişim algısını değeri de 55,94 puan olarak tespit edildi.

Sonuç: Bu çalışma ile günlük adım sayısının kendi başına fiziksel uygunluk ile direkt olarak ilişkilendirmenin güvenli bir yaklaşım olamayacağı, yalnızca günlük 9,500 adımın fiziksel uygunluğun net bir göstergesi olarak kabul etmek yerine kalp hızı, kalori harcanması gibi farklı parametrelerin de eklenmesi ile daha kesin yargılara ulaşılabileceği kanısına ulaşılmıştır. Ayrıca katılımcıların yaşam kalitesi algılarının fiziksel uygunlukları ile ilişkilendirilebilmesi için ilerleyen yıllarda gerçekleştirilecek çalışmalar ile desteklenmesi gerektiğini düşündürtmektedir.

Anahtar Kelimeler: Fiziksel uygunluk, yaşam kalitesi, pandemi, sağlık parametreleri

Introduction

The measures taken during the Coronavirus disease-2019 (COVID-19) pandemic and the remote implementation of education have led young people to spend less time on physical activity (PA) and become more sedentary. This situation poses a threat not only to the healthy physical fitness (PF) of young people but also may contribute to an increase in body mass index (BMI) and the early onset of various non-communicable chronic diseases (hypertension, myocardial infarction, lung disease, sleep apnea syndrome) (1), which can affect their quality of life (QoL) significantly.

PF is the ability to perform daily physical activities without harming people's physiological, psychological, and social health (2). As a fundamental health indicator at both individual and societal levels, PF includes anthropometric, metabolic, and neuromotor variables from a physiological perspective (3). PF is positively associated with PA (4), meaning that the higher the level of PA, the better the individual's PF (5). Evidence has shown that regular PA is inversely associated with overweight and obesity (6). When PA is insufficient, sedentary living time increases, leading to the deterioration of health and motor performance (7). To cope with this situation, children and adolescents are recommended to engage in moderate to vigorous PA for at least 60 minutes (8), while in the analysis of PA levels, it is emphasized that the importance of taking more than 9,500 steps per day for healthy living and PF (9).

BMI is widely used to measure inadequate nutrition, overweight, and obesity and is considered a global health indicator (10,11,12). Although some studies have claimed that BMI could effectively reflect the PF of ordinary university students (13), others have discussed the relationship between various components of PF and BMI in children (14) and adolescents (15). Therefore, monitoring the BMI of students is of great importance for understanding their physical development, but it is not clear whether using only the BMI index in the PF assessment reflects students' PF and health.

The World Health Organization (WHO) defines the QoL as the perception of an individual's position in life about their culture and value systems, goals, expectations, standards, and concerns. QoL is influenced by various factors such as physical and mental health, level of independence, social relationships, personal beliefs, and environmental conditions. It is a theoretical framework used to evaluate the living conditions of diverse communities (16). The short form-36 (SF-36) is a widely accepted and standardized tool used to measure health-related QoL (17).

Numerous articles have been published on both remote education and students' physiological conditions related to the COVID-19 pandemic (18,19,20,21,22), but there are limited publications that examine the situation developing after the pandemic (23,24). Monitoring all these changes in physiological parameters is necessary not only as a stop and detection but also to facilitate predicting negative situations that may occur in the future.

This study aims to collect data on the physiological and health-related QoL of my students who are studying in seven different programs in the 2021-2022 academic year, where a gradual exit from pandemic conditions and face-to-face education began, and to determine their PF and QoL perceptions, to evaluate these basic parameters from a physiological perspective by identifying the relationship between these basic parameters, if any, and to create a basis for other studies to be conducted in the future.

Material and Methods

Participants:

Data from a total of n=213 students from 7 different programs studying at İstanbul University-Cerrahpaşa, Vocational School of Health Services (I.U-C, VSHS) in the 2021-2022 academic year were collected through a survey application. Surveys that were not filled out completely were not included in the database. No identification information was recorded from the participants, and the survey was completely anonymous and based on voluntary participation, so no consent form was required from the participants.

Measurements and Procedures:

Survey application:

The survey was conducted with the permission of the I.U-C, VSHS administration and was completely anonymous. The survey form was conducted through I.U-Cerrahpaşa's official survey portal. The LimeSurvey-based survey portal is a free and open-source online statistical survey web application. On the survey's welcome page, participants were instructed on how to fill out the form. The implementation of the survey was left open-ended, and a detailed explanation was provided about the objectives, the survey structure, the compilation method, and the anonymity of the test. The study was approved by the Local Ethics Committee of İstanbul Yeni Yüzyıl University (2023/02-1042).

It consists of two main parts:

(1) Survey questions related to socio-demographic characteristics: Consisting of questions collecting information on age, weight, height, and mean daily step count as indicator of PA. Participants were asked to provide the daily step count data collected by their smart phones. BMI (kg/m^2) was calculated using these measurements. According to the BMI values recommended by the WHO, students were divided into four categories representing thin, normal weight, overweight, and obese individuals with BMI values of <18.5 kg/m^2, 18.5-23.9 kg/m^2, 24-27.9 kg/m^2, and ⩾28 kg/m^2, respectively (13).

(2) QoL survey (SF-36): The SF-36 Health Survey is a standardized and widely used tool for assessing HRQOL worldwide. SF-36 has 36 items in 8 sections: Eight question scales; physical function (10 items), physical role limitation (4 items), emotional role limitation (3 items), vitality (4 items), mental health (5 items), social function (2 items), pain (2 items), and general health perceptions (5 items). Each scale consists of 2-10 questions, and low scores indicate low HRQOL. The Turkish validity and reliability study of the scale was conducted by Koçyiğit et al. (25).

Except for the second question of the scale, the other questions are evaluated considering the individuals' conditions in the last 4 weeks. The second question focuses on the participants' general perception of changes in their health in the last year. The 4th and 5th questions of the scale are answered in yes/no format, while the Likert-type rating is used for other health items. The subscales are evaluated on a 0-100 scale.

Statistical Analysis

To confirm the normality of the variables, the Kolmogorov-Smirnov test was used. The data of non-parametric variables were normalized using Blom's normal score transformation. Mean, standard deviation (SD), minimum, and maximum values were used to characterize the sample by gender in the descriptive analysis. Student's t-test was applied to compare the means of the groups. The comparison of PF variables according to compliance or non-compliance with PA recommendations was confirmed using covariate analysis adjusted for gender. A significance level of $p<0.05$ was determined for all tests. Statistical analysis was performed using GraphPad Prism v.8.0.1 software.

Findings

When looking at the participants, 64 male, and 149 female students took part in the study. The reported values of the participants showed a significant difference in body composition that could be considered representative of Türkiye as a whole. When comparing BMI values, it was observed that the proportion of male students was significantly higher than that of female students. The daily step count, which is considered an indicator of physical fitness, was higher in men than in women, but no significant difference was observed due to the high SD rates caused by very different minimal and maximal values (Table 1).

When looking at the distribution of BMI values among male and female participants, it was observed that the total percentage of overweight and obese men was higher than that of male participants (Table 2). Although the average step count of male participants was higher than that of female participants, there was a 10% excess of overweight and obese men in their percentages.

In terms of determining the quality of life, when looking at the criteria used, it was observed that the participants rated their physical functions as quite good (88.86 points). When looking at the other criteria, it was found that the average scores for physical role limitations (51.24), emotional role limitations (47.19), vitality (46.39), mental health (48.08), and social functioning (53.34) were all in the average range. One of the most interesting findings was that the general health perception score remained low at 38.37 (Table 3).

The value of the second question of the scale, which refers to the general perception of health changes in the past year, was also determined to be 55.94 points.

Discussion

Numerous studies have been conducted about students whose movement has been restricted and who have had to follow their classes and even exams from computers and/or smart devices during the pandemic period, but studies identifying the situation of students in the post-pandemic period are still being carried out. The success of students in school life is closely related to their physical fitness, quality of life, and overall well-being. It is clear that these factors, which can directly affect student success, are the result of a combination of emotional, behavioral, and cognitive

Table 1. Demographic characteristics of the participants and physical activity values

	Male					Female					p-value	Significance
	n	Avg.	SD	Lowest	Highest	n	Avg.	SD	Lowest	Highest		
Age (years)	64	20.34	1.56	18	24	149	19.88	1.152	18	25	0.0345	*
Length (cm)	64	176.6	5.51	167	188	149	161.3	6.04	152	173	<0.0001	***
Body weight (kg)	64	75.32	15.89	50	115	149	58.67	11.68	46	100	<0.0001	***
BMI (kg/m^2)	64	24.11	4.91	17	35	149	22.53	4.03	18.25	35.43	0.024	*
Step (daily avg)	64	9921	7961	800	30000	149	7338	7761	300	24600	0.6738	

Values are given as mean and standard deviation (SD). *p<0.05, ***p<0.001, BMI: Body mass index

Table 2. Body mass index (BMI) rates of participants

BMI ratio (%)	Male	Female
Slim	7.69	11.61
Normal weight	58.47	63.87
Excess weight	13.84	18.07
Obese	20	6.45

Values are given as percentages (%)

Table 3. Quality of life index values of participants

Criterion	Substance	Avg	SD
Physical function	10	88.86	10.76
Physical role constraint	4	51.24	13.19
Emotional role limitation	3	47.19	6.74
Wellness	4	46.39	7.63
Mental health	5	48.08	14.19
Social function	2	53.34	8.23
Pain	2	58.00	31.05
General perception of health	5	38.37	12.88

Values are given as mean and standard deviation (SD)

dimensions on a physiological basis. Smartphones have now reached a level of necessity, even addiction, especially among young individuals, and this situation is reported to cause many undesirable conditions such as depression, anxiety disorders, substance use, musculoskeletal disorders, and sleep problems. Some studies indicate that this situation can negatively affect the QoL and PF (26,27).

Despite all these negative aspects, smartphones and other devices that work with them are widely used today. One of their usage areas covers the healthcare field, and many personal health parameters are measured through these devices. This sector, which is developing with increasing diversity and measurement reliability, is causing important developments in the field of health sciences. Smartphones have also begun to be the subject of many studies in the field of health sciences (28,29).

Many data that can be associated with health can be collected through systems such as accelerometers and gyroscopes within these devices. These data are data that can be used to detect and monitor FU (3). FU is one of the most important indicators of healthy growth and development in children affected by different PA levels. Although it can provide more accurate and reliable data on PA density when measured objectively (30), this study aimed to determine whether a connection could be established between daily step count, a simple PA value obtained from participants' smart devices, and FU, assuming that the data obtained from students' smart devices could provide reliable data on physical fitness. However, it was found that although the percentage of overweight and obese male participants was higher, their average step counts were higher than those of female participants. When the step counts of overweight and obese individuals were compared within themselves, no significant correlation was observed. This finding contradicts a study by Bovet et al. (31), which showed a strong inverse relationship between overweight and various standardized PF tests in adolescents in an African country.

From a physiological perspective, this inverse relationship is consistent with low PA being a possible determinant of obesity in this sample of adolescents. Considering that the physical function criterion has the highest score on the QoL index, and the physical role limitation criterion is slightly above 50 points, it can be thought that the participants' QoL is good in terms of their physical fitness, but it should also be considered that the fitness score is below 50 points.

The WHO defines the QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and concerning their goals, expectations, standards, and concerns". This perception can be more positive or negative depending on the meanings that individuals attach to their life experiences. Attributing a positive value and meaning to life experiences, even in the face of difficulties, is a fundamental characteristic of resilient individuals (32). In our study, I.U-C, VSHS students gave average scores for their general quality of life. Perhaps

one of the most interesting findings is that the perceived general change in health over the past year was rated at 55.94, while the overall health perception scores remained low at 38.37. Indeed, average scores for emotional role limitation, mental health, and social functioning criteria also support this perception. This situation may have arisen from various reasons. While returning to school after the pandemic period was seen positively by the students, the fact that the health perception score was below 40 in the past four weeks may reflect the influence of recent environmental factors.

Study Limitations

The analysis of more data, which can be obtained by enriching the data obtained from the participants, can help to establish a connection between the QoL and physical fitness.

Conclusion

This study suggests that daily step count alone is not a safe approach to directly correlate with PF and that adding other parameters such as heart rate and calorie expenditure can lead to more accurate conclusions. Furthermore, it is necessary to support the perception of the participant's QoL with studies to be carried out in the coming years to correlate it with their physical fitness.

Contributions: I would like to thank my students for their contributions to this study.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of İstanbul Yeni Yüzyıl University (2023/02-1042).

Informed Consent: No identification information was recorded from the participants, and the survey was completely anonymous and based on voluntary participation, so no consent form was required from the participants.

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References

1. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. JAMA Cardiol. 2018;3:280-287. [Crossref]
2. Davison KK, Werder JL, Lawson CT. Children's active commuting to school: current knowledge and future directions. Prev Chronic Dis. 2008;5:100. [Crossref]
3. Plasqui G, Westerterp KR. Accelerometry and heart rate as a measure of physical fitness: proof of concept. Med Sci Sports Exerc. 2005;37:872-876. [Crossref]
4. Gassmann NN, Matthes KL, Eppenberger P, Brabec M, Panczak R, Zwahlen M, et al. Residential Altitude Associates With Endurance but Not Muscle Power in Young Swiss Men. Front Physiol. 2020;11:860. [Crossref]
5. Ørntoft C, Larsen MN, Madsen M, Sandager L, Lundager I, Møller A, et al. Physical Fitness and Body Composition in 10-12-Year-Old Danish Children in Relation to Leisure-Time Club-Based Sporting Activities. Biomed Res Int. 2018;2018:9807569. [Crossref]
6. Dias PJ, Domingos IP, Ferreira MG, Muraro AP, Sichieri R, Gonçalves-Silva RM. Prevalence and factors associated with sedentary behavior in adolescents. Rev Saude Publica. 2014;48:266-274. [Crossref]
7. Bürgi R, de Bruin ED. Differences in Spatial Physical Activity Patterns between Weekdays and Weekends in Primary School Children: A Cross-Sectional Study Using Accelerometry and Global Positioning System. Sports (Basel). 2016;4:36. [Crossref]
8. Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, et al. Evidence based physical activity for school-age youth. J Pediatr. 2005;146:732-737. [Crossref]
9. Matsudo VK, Ferrari GL, Araújo TL, Oliveira LC, Mire E, Barreira TV, et al. [Socioeconomic status indicators, physical activity, and overweight/obesity in Brazilian children]. Rev Paul Pediatr. 2016;34:162-170. [Crossref]
10. Zhang Y, Su F, Song Y, Lu J. Associations between Physical Fitness Index and Body Mass Index in Tibetan Children and Adolescents in Different High-Altitude Areas: Based on a Study in Tibet, China. Int J Environ Res Public Health. 2022;19:10155. [Crossref]
11. Dong Y, Lau PWC, Dong B, Zou Z, Yang Y, Wen B, et al. Trends in physical fitness, growth, and nutritional status of Chinese children and adolescents: a retrospective analysis of 1·5 million students from six successive national surveys between 1985 and 2014. Lancet Child Adolesc Health. 2019;3:871-880. [Crossref]
12. Bi C, Yang J, Sun J, Song Y, Wu X, Zhang F. Benefits of normal body mass index on physical fitness: A cross-sectional study among children and adolescents in Xinjiang Uyghur Autonomous Region, China. PLoS One. 2019;14:e0220863. [Crossref]
13. Chen X, Cui J, Zhang Y, Peng W. The association between BMI and health-related physical fitness among Chinese college students: a cross-sectional study. BMC Public Health. 2020;20:444. [Crossref]
14. Karppanen AK, Ahonen SM, Tammelin T, Vanhala M, Korpelainen R. Physical activity and fitness in 8-year-old overweight and normal weight children and their parents. Int J Circumpolar Health. 2012;71:17621. [Crossref]
15. Cho M, Kim JY. Changes in physical fitness and body composition according to the physical activities of Korean adolescents. J Exerc Rehabil. 2017;13:568-572. [Crossref]
16. WHO, The World Health Organization Quality of Life (WHOQOL). 2012. [Crossref]
17. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-483. [Crossref]
18. Reinhart A, Malzkorn B, Döing C, Beyer I, Jünger J, Bosse HM. Undergraduate medical education amid COVID-19: a qualitative analysis of enablers and barriers to acquiring competencies in distant learning using focus groups. Med Educ Online. 2021;26:1940765. [Crossref]
19. Aydın C, Tarhan Ç. Distance Education Adaptation of Vocational High School Students within the Digital Divide. Alphanumeric Journal. 2018;6:349-364. [Crossref]
20. Akbaş Tosunoğlu E, Gayef A, Arslan E, Vardar SA. Opinions of Physiology Postgraduate Students and Residents About Physiology Education in Medical Faculties in Turkey. Tıp Eğitimi Dünyası. 2022;21:26-41. [Crossref]
21. Köse E, Eerbiçer H, Shahim AM, Çakmak A, Derici A, Hoşseven A, Koçer E, et al. Attitudes of Medical Faculty Students towards Distance Education and Related Factors during the Pandemic Period. Online Turkish Journal of Health Sciences. 2021;6:453-460. [Crossref]

22. Çakmakkaya ÖS, Demirbaş KC, Yaman MO, Erginöz E. School of Evidence-Based Medicine: The Cerrahpaşa Medical Faculty Practice of Evidence-Based Medicine Training. Cerrahpaşa Medical Journal. 2021;45:33-42. [Crossref]
23. Patin A, Ladner J, Tavolacci MP. Change in University Student Health Behaviours after the Onset of the COVID-19 Pandemic. Int J Environ Res Public Health. 2022;20:539. [Crossref]
24. Pyšná J, Pyšný L, Cihlář D, Petrů D, Müllerová LH, Čtvrtečka L, et al. Physical Activity and BMI before and after the Situation Caused by COVID-19 in Upper Primary School Pupils in the Czech Republic. Int J Environ Res Public Health. 2022;19:3068. [Crossref]
25. Koçyiğit H, Aydemir O, Fişek G, Ölmez N. Form-36 (KF-36)'nın Türkçe versiyonunun güvenilirliği ve geçerliliği. İlaç ve Tedavi Dergisi. 1999;12:102-106. [Crossref]
26. Cheng C, Cheung MWL, Wang HY. Multinational comparison of internet gaming disorder and psychosocial problems versus well-being: Meta-analysis of 20 countries. Comput Hum Behav. 2018;88:153-167. [Crossref]
27. Tran BX, Huong LT, Hinh ND, Nguyen LH, Le BN, Nong VM, et al. A study on the influence of internet addiction and online interpersonal influences on health-related quality of life in young Vietnamese. BMC Public Health. 2017;17:138. [Crossref]
28. Dorsey ER, Yvonne Chan YF, McConnell MV, Shaw SY, Trister AD, Friend SH. The Use of Smartphones for Health Research. Acad Med. 2017;92:157-160. [Crossref]
29. Miralles I, Granell C, Díaz-Sanahuja L, Van Woensel W, Bretón-López J, Mira A, et al. Smartphone Apps for the Treatment of Mental Disorders: Systematic Review. JMIR MHealth Uhealth. 2020;8:e14897. [Crossref]
30. Estivaleti JMO, Bergamo RR, Oliveira LC, Beltran DCG, Silva Junior JPD, Santos MD, et al. Physical activity level measured by accelerometry and physical fitness of schoolchildren. Rev Paul Pediatr. 2022;41:e2021230. [Crossref]
31. Bovet P, Auguste R, Burdette H. Strong inverse association between physical fitness and overweight in adolescents: a large school-based survey. Int J Behav Nutr Phys Act. 2007;4:24. [Crossref]
32. Park CL. The Meaning Making Model: A Framework for understanding meaning, spirituality, and stress-related growth in health pyschology. The European Health Psychologist 2013;15:40-47. [Crossref]

ORIGINAL ARTICLE

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The Effectiveness of Appendicitis Inflammatory Response Score in the Evaluation of Acute Appendicitis: A Meta-analysis

Akut Apandisit Değerlendirmesinde Apandisit Enflamatuvar Yanıt Skorunun Etkinliği: Meta-analiz Çalışması

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ABSTRACT

Background: One of the most frequent causes of urgent abdominal diseases is appendicitis. Various diagnostic methods are used in the diagnosis of appendicitis, scoring systems are among them. We aimed to meta-analyze the studies evaluating the effectiveness of the appendicitis inflammatory response-score (AIR-S). In light of the studies done on the topic, it was intended to highlight the diagnostic benefits of scoring, which allow for the simultaneous evaluation of clinical, laboratory, and imaging findings as well as the patient's medical history, and to add to the literature.

Materials and Methods: All studies published in the last 15 years using the terms "All fields=appendicitis inflammatory response" (AND), "All fields=receiver operating characteristic" (AND) in Web of Science Core Collection, PubMed and Google Scholar databases were searched, systematic review and meta-analysis were performed.

Results: Thirteen publications were included in the study according to inclusion and exclusion criteria. It was noted that the studies were conducted on 8.052 patients with a mean age of 30.00 and gender distribution as 48.00% male and 52.00% female. The cut-off point of the studies was found to be 5.00, Sensitivity 85.00%, Specificity 59.00%. The studies were homogeneous (I^2=19.830; Cochran Q=14.968; p>0.05). AIR-S diagnostic distinguish ability was statistically significant (total-fixed effects=0.838; 95% confidence interval 0.800-0.875; p<0.001). There was no statistically significant publication bias (p>0.05).

Conclusion: In this study, the sum of the values determined for the diagnostic parameters of AIR-S was below 170. This finding result that using AIR-S alone to diagnose acute appendicitis is insufficient, and that it is preferable to utilize it in conjunction with other diagnostic measures.

Keywords: Appendicitis, appendicitis inflammatory response score, receiver operating characteristic, bias

ÖZ

Amaç: Acil karın hastalıklarının en sık nedenlerinden biri apandisittir. Apandisit tanısında çeşitli tanı yöntemleri kullanılmaktadır, skorlama sistemleri de bunlar arasındadır. Apandisit enflamatuvar yanıt-skorunun (AIR-S) etkinliğini değerlendiren çalışmaları meta-analiz tekniği ile değerlendirmek hedefledi. Konuyla ilgili yapılan çalışmalar ışığında, klinik, laboratuvar ve görüntüleme bulgularının yanı sıra hastanın tıbbi öyküsünün de eş zamanlı olarak değerlendirilmesine olanak sağlayan skorlamanın tanısal faydalarını vurgulamak ve literatüre katkıda bulunmak amaçlandı.

Gereç ve Yöntemler: Web of Science Core Collection, Pubmed ve Google Scholar veri tabanlarında "All fields=appendicitis inflammatory response" (VE), "All fields=receiver operating characteristic" (VE) terimleri kullanılarak son 15 yılda yayınlanmış tüm çalışmalar taranmış ve sistematik incelemesi ve meta-analizi yapıldı.

Bulgular: Çalışmaya dahil etme ve dışlama kriterlerine uygun olarak on üç yayın dahil edildi. Çalışmaların 8,052 hasta üzerinde yapıldığı, yaş ortalamasının 30 olduğu, cinsiyet dağılımının %48 erkek ve %52 kadın olduğu görüldü. Çalışmaların kesim noktası 5, duyarlılık %85, özgüllük %59 olarak bulundu. Çalışmalar homojendi (I^2=19,830; Cochran Q=14,968; p>0,05). AIR-S tanısal ayırt etme yeteneği istatistiksel olarak anlamlıydı (toplam-sabit etki=0,838; %95 güven aralığı 0,800-0,875; p<0,001). İstatistiksel olarak anlamlı yayın yanlılığı bulunmadı (p>0,05).

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ÖZ

Sonuç: Bu çalışmada, AIR-S'nin tanısal parametreleri için belirlenen değerlerin toplamı 170'in altındadır. Bu bulgu, AIR-S'nin akut apandisit tanısında tek başına kullanılmasının yetersiz olduğunu ve diğer tanısal ölçümlerle birlikte kullanılmasının daha uygun olduğunu ifade etmektedir.

Anahtar Kelimeler: Apendisit, apandisit enflamatuvar yanıt skoru, alıcı işlem karakteristiği, yanlılık

Introduction

One of the most frequent causes of urgent abdominal diseases is appendicitis. It is known that acute appendicitis (AA) affects 90-100/100,000 people in developed countries (1). If appendicitis is suspected in a patient presenting with acute abdominal symptoms, the diagnosis should be confirmed before performing emergency surgery. Rapid and accurate diagnosis is of great importance to reduce the complications of AA and even to decrease the mortality rates that may occur due to complications. For many other reasons (pregnancy, hematologic origin etc.), obtaining a reliable preoperative diagnosis may be difficult even for physicians and/or experienced surgeons (2,3).

Clinicians have developed various scoring tools with prognostic value based on the principle of evaluating many clinical findings together in order to minimize the margin of error in the diagnosis of AA and to confirm the preliminary diagnosis. Among these scores, Alvarado, Modified Alvarado, Lintula, Tzanakis, appendicitis inflammatory response score (AIRS), Ohmann, Fenyo-Lindberg and Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) aim to improve diagnostic ability and reduce the rate of negative appendicectomy (4). Recently, scoring models have been reported to predict complicated acute appendicitis. Scoring systems that combine clinical and imaging features and scoring models that can be calculated using predictive equations have been proposed (5,6,7,8).

Important clues for AA can be obtained through tools that assess risk according to a score obtained by combining patients' symptoms, clinical findings and laboratory results, and even calculating according to their severity and level. The appendicitis inflammatory response-score (AIR-S), one of these instruments, was created in 2008 and is currently the most used pre-operative tool. The World Society for Emergency Surgery's 2020 clinical practice suggests using AIR-S for the diagnosis and management of AA (9).

In this study, we aimed to meta-analyze the studies evaluating the effectiveness of the AIR-S. In the light of these studies, it was aimed to draw attention to the diagnostic values of scoring, which enables the evaluation of clinical, laboratory and imaging methods together as well as the history obtained from the patient, to emphasize the importance of its use in daily practice and to contribute to the literature.

Material and Methods

The preferred PRISMA reporting elements for systematic reviews and meta-analyses were followed when conducting this investigation. This study's execution did not require ethical approval.

Keywords and Search Strategy

In this study, studies using AIR-S in patients with AA and evaluating the diagnostic value of this score according to receiver operating characteristic (ROC) were analyzed. All studies published in the last 15 years using the terms "All fields=appendicitis inflammatory response" (AND), "All fields= ROC" (AND) in Web of Science Core Collection, PubMed and Google Scholar databases (accessed March, April and May 2023) were searched and systematic review and meta-analysis were performed.

AIRS

Vomiting, right iliac fosse-migrating abdomen pain, rebound tenderness, fever (°C), leukocyte count (PML), white blood cell count (WBC 10^9/L), and C-reactive protein (CRP) (mg/L) concentration are all considered indications for AIR-S. Each evaluation criterion has a score determined for the severity of the evaluation. Accordingly; vomiting (score: 1), abdominal pain that migrates to the right iliac fossa (score: 1), rebound tenderness or muscular defense (Light: 1, Moderate: 2, Strong: 3), fever of 38. 5 °C or more (score: 1), PML (70-84%: 1, ⩾85%: 2), WBC (10.0-14.9 x 10^9/L: 1, ⩾15.0x10^9/L: 2), CRP (10-49 g/L: 1, ⩾50 g/L: 2). The assessment results in a final score ranging from 0 to 12. A total score between "0-4" means "low probability follow-up", "5-11" means "re-evaluation/outpatient follow-up" and "9-12" means "high probability/surgical exploration" (9).

Inclusion and Exclusion Criteria

The inclusion criteria were that the studies were conducted in adult patients, published in the last fifteen years, the diagnosis was acute appendicitis, the AIR Score efficiency was performed by applying ROC analysis, the area

under the curve (AUC) value and the standard error/95% confidence interval were calculated accordingly.

Exclusion criteria were defined as not including one or more of the inclusion criteria, studies in pediatric patients, case reports, systematic reviews, conference reports, animal experiments and missing data in ROC analysis results.

Outcome Measures

For the effectiveness of AIR scores on clinical decision-making, we used all calculated and reported ROC analysis results within the total number of cases in the studies.

Data Extraction and Assessment of Quality

A total of 315 studies were accessed in line with the search strategies. The researchers who planned the study (four independent researchers with academic qualifications in general surgery, emergency medicine, and family physician specialists) checked the "Title" and "Abstract" parts of the retrieved articles for compliance with the study strategies. At the end of all search and control processes, all data were recorded by the researchers on the designed data collection forms and all records were collected under a common file. The findings of a total of 13 studies that met the inclusion criteria were statistically evaluated. Figure 1A displays the study's PRISMA flow diagram.

Statistical Analysis

Studies obtained through this systematic review were considered meta-analysis. Heterogeneity between studies I^2 and the risk of publication bias were investigated with Funnel Chart and Egger's Regression. In the included studies, the Cochrane Risk of Bias technique, which evaluates the presence of bias with seven criteria, was used. According to this technique, each study was evaluated according to the "low, unclear, high" bias criteria (10). The threshold value of 0.25 for the I^2 value and 0.05 for statistical significance was accepted to determine whether heterogeneity was present. Calculations were performed with Medcalc (version 20.218 Free-Trial) and Meta-DISC (version 1.4) program.

Results

After a database search, a total of 315 articles containing patient data related to AIR-S were found. Thirteen publications in total were included in the study for evaluation after taking the inclusion and exclusion criteria into account. The articles' titles and abstracts were read, and it was determined whether they were pertinent to the topic. The PRISMA flow chart of the study is shown in Figure 1A. Seven criteria were used to assess the risk of bias. Each study was assessed as low risk, high risk or unclear risk of bias. The highest risk was "blinding of participants and personnel" and the lowest risk was "allocation concealment" (Figure 1B).

It was seen that 13 studies using ROC curve, a statistical technique for performance measurement of AIR-S, were conducted with a total of 8.052 patients, 48% were male, 52% were female, and the mean age of all patients was 30 years. When the common features of the studies were analyzed, the cutoff point was found to be 5, sensitivity

Figure 1. **(A)** PRISMA methodological quality summary study flow diagram with AIR-S. **(B)** Risk of bias graph: risk of bias item presented across all included studies

ROC: Receiver operating characteristic

86.90%, specificity 53.80% (n=10). While the 3 studies aimed to show the clinical efficacy of the AIR-S with ROC analysis results, they did not share the cutoff point and the sensitivity analysis results related to this point (Table 1).

The clinical efficacy of AIR-S was evaluated in 13 included studies. For the calculation of the standard error, it was extended with five to all cell counts in all runs to avoid division with zero error. Homogeneity was observed in the studies (I^2=19.830; Cochran Q=14.968; p=0.243). According to the results, the area under the curve of AIR-S was statistically significant (total-fixed effects=0.838; 95% confidence interval 0.800-0.875; p<0.001; Figure 2A). The summary receiver operating characteristic (sROC) curve, which is shaped according to the common results of the studies and includes the sensitivity analysis values, is presented in Figure 2B. AIR-S diagnostic distinguishability was statistically significant (p<0.001).

There was no statistically significant publication bias (p=0.191). Funnel graps shows the symmetrical, the likely it is not that of bias will be substantial (Figure 3).

Discussion

Today, patients can present with symptoms of AA at any time of the day to the emergency department, general surgery outpatient clinic or family medicine centers of healthcare facilities. It is important for physicians to rely on clinical scoring systems during off-hours (nights, weekends, holidays) when access to imaging services (especially ultrasonography) is difficult. In this study, we aimed to examine the diagnostic efficacy of the AIR-S developed for the combined evaluation of clinical and laboratory parameters in the diagnosis of AA by meta-analysis.

The AIR-S has been accepted as one of the best-performing scores for the diagnosis of AA among the various clinical prediction tools available. AIR-S with other scoring systems can significantly reduce the risk of overdiagnosis of AA and thus provide a reliable diagnostic performance, while at the same time enabling treating surgeons to avoid the routine use of computed tomography (24).

The results obtained from validation studies were summarized and it was shown that the AIR-S had an area under the ROC curve (AUC) of 0.84, sensitivity (92%), specificity (63%), The AIR score performed best performance compared to other scoring systems (Alvarado, PIRASA, Ohmann, Eskelinen, Lintula, Modified Alvarado) in terms of sensitivity, specificity AUC values and usability (25). However, it is recommended that the sum of the sensitivity and specificity of the tests that should be used for diagnosis should be above 170 (26). In our study, the sum of the values determined for the diagnostic parameters of the AIR-S was below 170. This result indicates that the use of the AIR-S alone in the diagnosis of AA is not a sufficient diagnostic tool and that it is more appropriate to use it together with other parameters that help the diagnosis.

The AIR-S is a valid decision support system for clinical diagnosis and has high sensitivity for complicated appendicitis. In addition, it was emphasized that the AIR-S had a high discrimination capacity in children and patients with long-term symptoms and performed equally well in both sexes (13).

It has been stated that the diagnostic accuracy of the RIPASA system, which is used in the literature as one of the

Table 1. Statistical characteristics of AIR-S studies

Study	n	M/F	Age	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Ak et al. (11)	232	105/127	Median: 33	≥5	94.39 (88.19-97.92)	26.13 (18.25-35.32)
Andersson et al. (12)	229	105/124	Mean: 23.40	>4	93.00 (89.00-97.00)	71.00 (65.00-77.00)
Andersson et al. (13)	3878	1802/2076	Median: 26.10	<6	96.10	43.00
Andrade et al. (14)	292	183/109	-	<6	94.70 (80.40-98.3)	76.50 (74.2-90.30)
Birben et al. (15)	237	126/111	Mean: 34.00	>4	80.62 (72.74-87.05)	57.14 (28.86-82.34)
Bokade et al. (16)	90	62/28	Mean: 32.14	-	-	-
Chae et al. (17)	189	63/126	Mean: 33.00	>4	52.50 (39.30-65.40)	72.70 (64.10-80.20)
Gadahire et al. (18)	100	55/45	Mean: 25.89	≥5	100.00	55.00
Haak et al. (19)	956	486/470	Mean: 28.00	≥5	64.50	63.67
March et al. (20)	98	41/57	Median: 30.00	-	-	-
Martín-Del Olmo et al. (21)	458	266/192	Median: 31.00	-	-	-
Sammalkorpi et al. (22)	829	-	Median: 32.00	≥5	83.10	63.10
Scott et al. (23)	464	172/292	Mean: 27.00	≥5	90.00 (84.00-95.00)	63.00 (58.00-68.00)

CI: Confidence interval, AIR-S: Appendicitis inflammatory response-score

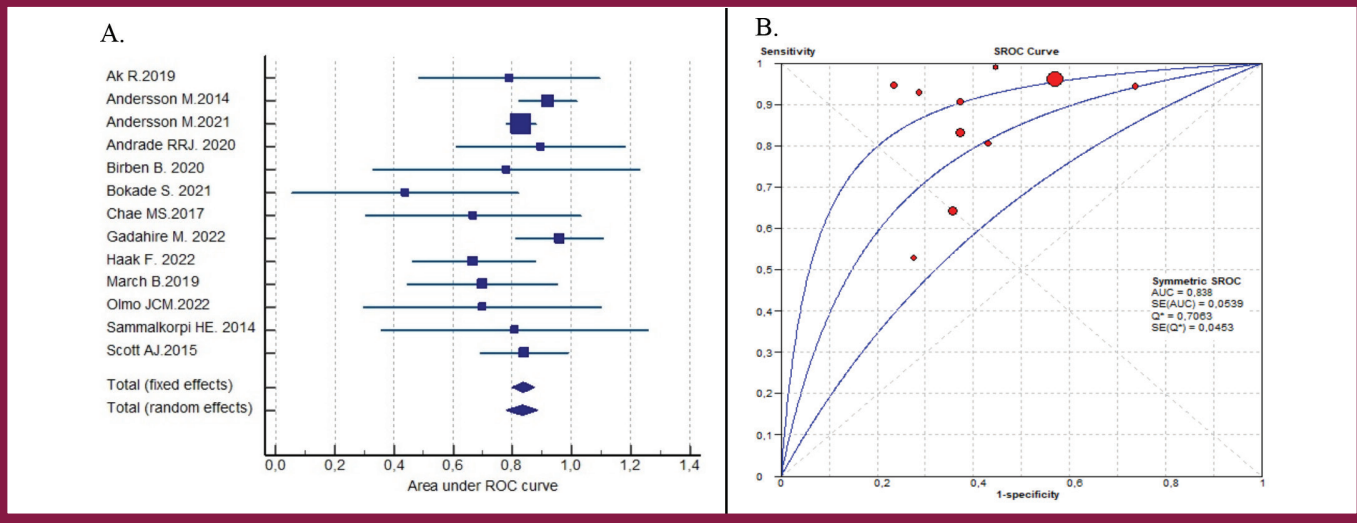

Figure 2. **(A)** Forest graph of ROC analyses of AIR-S studies. **(B)** sROC curve of studies included in the systematic review on AIR-S

AIR-S: Appendicitis inflammatory response-score, ROC: Receiver operating characteristic, SROC: Summary receiver operating characteristic, AUC: Area under the curve

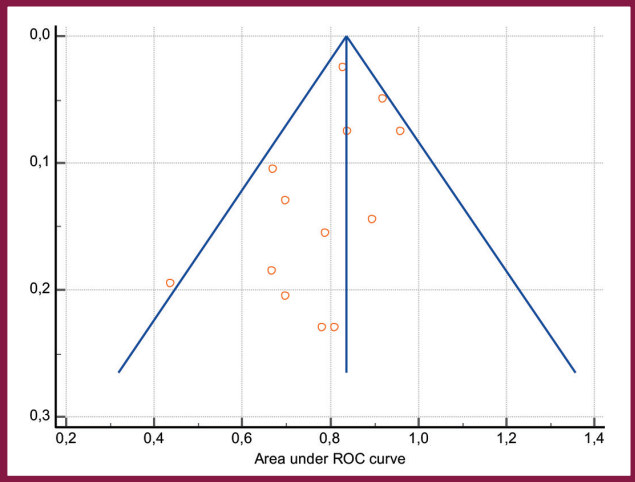

Figure 3. Funnel graph for ROC analysis of AIR-S studies

AIR-S: Appendicitis inflammatory response-score, ROC: Receiver operating characteristic

scoring systems, is better than the Alvarado and AIR scores, but the single-center study is a disadvantage because the results differ for region and ethnicity (20).

It was determined that Alvarado and AIR-S, which are most commonly used in the diagnosis of AAin pregnant women, are effective methods in the diagnosis of AA. However, the higher accuracy of AIRS, which includes CRP value, suggests that this system is an advantage (27).

In line with the results of this meta-analysis, it can be said that patients evaluated with the AIR-S can be discharged with detailed information (if the complaints of pain, nausea, vomiting, etc. do not go away and worsen, they should apply to the emergency department again) if the total score of the patients evaluated with the AIR-S is below 5, knowing that re-evaluation and careful follow-up are essential in case of change and/or worsening of symptoms. Recent studies have also shown that antibiotics as a non-operative treatment method have a low morbidity and treatment success rate after 30 days of follow-up (28,29).

AIR-S can be particularly useful in environments and situations where imaging methods are limited or unavailable and resources are scarce. The risk stratification of patients with suspected AIR-S AA can guide the decision-making process to optimize the utility of diagnostic imaging and avoid negative and unnecessary investigations.

Conclusion

The AIR-S has significant diagnostic efficacy in the diagnosis of AA. Risk stratification of patients with suspected AA according to the AIR-S can guide decision-making to reduce admissions, optimize the utility of diagnostic imaging, and avoid adverse and unnecessary explorations. Physician confidence in clinical scoring systems is also important.

However, in this study, the sum of the values determined for the diagnostic parameters of AIR-S was below 170. This result indicates to clinicians that the AIR-S alone is not an adequate diagnostic tool in the diagnosis of AA and that it is more appropriate to use it in conjunction with other diagnostic parameters.

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Ethics

Ethics Committee Approval: Ethics committee approval was not required as it was a meta-analysis study.

Informed Consent: Not required as it was a meta-analysis study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.G., D.S., S.Ö., N.B., Concept: İ.G., D.S., Design: İ.G., D.S., Data Collection or Processing: İ.G., D.S., N.B., Analysis or Interpretation: İ.G., D.S., N.B., Literature Search: İ.G., D.S., N.B., Writing: İ.G., D.S., S.Ö., N.B.

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References

1. Rodriguez A, Barraco RD, Ivatury RR. Geriatric Trauma and Acute Care Surgery. In: Anderson TN, Moore F, Jordan J, editors. Acute Appendicitis 2018. [Crossref]
2. Ellis H. The story of appendicitis and its treatment. J Perioper Pract. 2019;30:188. [Crossref]
3. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet. 2015;386:1278-1287. [Crossref]
4. Sharma K, Thomas S, Chopra A, Choudhury M. Evaluation of the Diagnostic Accuracy of Eight Reported Clinical Scoring Systems in the Diagnosis of Acute Appendicitis. Indian J. 2022;84:741-748. [Crossref]
5. Kobayashi T, Hidaka E, Koganezawa I, Nakagawa M, Yokozuka K, Ochiai S, et al. Development of a scoring model based on objective factors to predict gangrenous/perforated appendicitis. BMC Gastroenterol. 2023;23:198. [Crossref]
6. Atema JJ, van Rossem CC, Leeuwenburgh MM, Stoker J, Boermeester MA. Scoring system to distinguish uncomplicated from complicated acute appendicitis. Br J Surg. 2015;102:979-990. [Crossref]
7. Eddama M, Fragkos KC, Renshaw S, Aldridge M, Bough G, Bonthala L, et al. Logistic regression model to predict acute uncomplicated and complicated appendicitis. Ann R Coll Surg Engl. 2019;101:107-118. [Crossref]
8. Geerdink TH, Augustinus S, Atema JJ, Jensch S, Vrouenraets BC, de Castro SMM. Validation of a Scoring System to Distinguish Uncomplicated From Complicated Appendicitis. J Surg Res. 2021;258:231-238. [Crossref]
9. Andersson M, Andersson RE. The Appendicitis Inflammatory Response Score: A Tool for the Diagnosis of Acute Appendicitis that Outperforms the Alvarado Score. World J Surg. 2008;32:1843-1849. [Crossref]
10. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. [Crossref]
11. Ak R, Doğanay F, Akoğlu EU, Akoğlu H, Uçar AB, Kurt E, et al. Predictive value of scoring systems for the diagnosis of acute appendicitis in emergency department patients: Is there an accurate one? Hong Kong J Emerg Med. 2020;27:262-269. [Crossref]
12. Andersson M, Rubér M, Ekerfelt C, Hallgren HB, Olaison G, Andersson RE. Can new inflammatory markers improve the diagnosis of acute appendicitis? World J Surg. 2014;38:2777-2783. [Crossref]
13. Andersson M, Kolodziej B, Andersson RE. Validation of the Appendicitis Inflammatory Response (AIR) Score. World J Surg. 2021;45:2081-2091. [Crossref]
14. Andrade JRR, Rivas MVU, Cumbe JCO, Abad KMC, Medina PPN. Evaluación de la Escala de Alvarado versus Score de Respuesta Inflamatoria de la Apendicitis, Hospital José Carrasco Arteaga 2018. Revista Médica HJCA. 2020;12:2. [Crossref]
15. Birben B, Muge Sonmez B, Er S, Ozden S, Tugra Kosa M, Tez M. Comparison of diagnostic scoring systems with imaging methods for the diagnosis of acute appendicitis. Ann Med Res. 2020;27:3166-3170. [Crossref]
16. Bokade S, Verma A, Kumar S. Comparative Study of Modified Alvarado Score, Appendicitis Inflammatory Response Score and New Adult Appendicitis Score In Predicting The Accuracy Of Diagnosing Acute Appendicitis. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2021;20:16-35. [Crossref]
17. Chae MS, Hong CK, Ha YR, Chae MK, Kim YS, Shin TY, et al. Can clinical scoring systems improve the diagnostic accuracy in patients with suspected adult appendicitis and equivocal preoperative computed tomography findings? Clin Exp Emerg Med. 2017;20;4:214-221. [Crossref]
18. Gadahire M, Wadaskar S, Yadav RK. Prospective Study To Evaluate Appendicitis Inflammatory Response Score And Ct-Scan To Diagnose Acute Appendicitis International. Journal of Academic Medicine and Pharmacy. 2022;5:246-251. [Crossref]
19. Haak F, Kollmar O, Ioannidis A, Slotta JE, Ghadimi MB, Glass T, et al. Predicting complicated appendicitis based on clinical findings: the role of Alvarado and Appendicitis Inflammatory Response scores. Langenbecks Arch Surg.2022;407:2051-2057. [Crossref]
20. March B, Leigh L, Brussius-Coelho M, Holmes M, Pockney P, Gani J. Can CRP velocity in right iliac fossa pain identify patients for intervention? A prospective observational cohort study. Surgeon. 2019;17:284-290. [Crossref]
21. Martín-Del Olmo JC, Concejo-Cutoli P, Vaquero-Puerta C, López-Mestanza C, Gómez-López JR. Clinical prediction rules in acute appendicitis: which combination of variables is more effective at predicting? Cir Cir. 2022;90:42-49. [Crossref]
22. Sammalkorpi HE, Mentula P, Leppäniemi A. A new adult appendicitis score improves diagnostic accuracy of acute appendicitis-a prospective study. BMC Gastroenterol. 2014;14:114. [Crossref]
23. Scott AJ, Mason SE, Arunakirinathan M, Reissis Y, Kinross JM, Smith JJ. Risk stratification by the Appendicitis Inflammatory Response score to guide decision-making in patients with suspected appendicitis. Br J Surg. 2015;102:563-572. [Crossref]
24. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines World J Emerg Surg. 2020;15:27. [Crossref]
25. Kularatna M, Lauti M, Haran C, MacFater W, Sheikh L, Huang Y, et al. Clinical prediction rules for appendicitis in adults: which is best? World J Surg. 2017;41:1769-1781. [Crossref]
26. Wians FH. Clinical laboratory tests: which, why, and what do the results mean? Laboratory Medicine 2009;40:105-113. [Crossref]
27. Bardakçi O, Bahçecioğlu İB, Tatli F, Özgönül A, Güldür ME, Uzunköy A. Does one of the two most commonly used scoring systems have a decisive advantage over the other in diagnosing acute appendicitis in pregnant women? Medicine (Baltimore). 2023;102:e33596. [Crossref]

28. Podda M, Gerardi C, Cillara N, Fearnhead N, Gomes CA, Birindelli A, et al. Antibiotic Treatment and Appendectomy for Uncomplicated Acute Appendicitis in Adults and Children: A Systematic Review and Meta-analysis. Ann Sur. 2019;270:1028-1040. [Crossref]

29. Ceresoli M, Fumagalli C, Fugazzola P, Zanini N, Magnone S, Ravasi M, et al. Outpatient Non-operative Management of Uncomplicated Acute Appendicitis: A Non-inferiority Study. World J Surg. 2023;47:2378-2385. [Crossref]

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The Diagnostic Value of Procalcitonin in Differentiation of Exacerbation and Pneumonia in Patients with Idiopathic Pulmonary Fibrosis

İdiyopatik Pulmoner Fibrozis Hastalarında Alevlenme ve Pnömoni Ayrımında Prokalsitoninin Tanısal Değeri

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ABSTRACT

Background: It is often difficult to distinguish between acute exacerbations of idiopathic pulmonary fibrosis (IPF-AE) and pneumonia occurring in patients with IPF (IPF-PNA). Procalcitonin (PCT) is a highly specific biomarker for bacterial infections. The diagnostic value of PCT in differentiating IPF-AE and IPF-PNA was investigated in the study.

Materials and Methods: All hospitalized patients with IPF-AE and IPF-PNA between January 2015 and June 2018 were evaluated. Demographic data, C-reactive protein (CRP) and PCT levels, the duration of hospitalization was recorded.

Results: A total of 44 eligible patients were randomized into two groups at a 1:1 ratio. The PCT and CRP levels were significantly higher in IPF-PNA group than in IPF-AE group (1.727±3.549 ng/mL vs. 0.642±0.049 ng/mL, p<0.001 for PCT, and 148.4±97.7 mg/L vs. 55.4±47.2 mg/L, p<0.001 for CRP). The duration of hospitalization was longer in IPF-PNA group (15.18±8.3 days vs. 8.54±2.5 days, p=0.001) than in IPF-AE group. Furthermore, when 0.1065 ng/mL was accepted as the cut-off value for PCT, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.955, 0.773, 0.808, and 0.944, respectively. When 35 mg/L was accepted as the cut-off value for CRP, the sensitivity, specificity, PPV and NPV were 0.955, 0.500, 0.656 and 0.917, respectively.

Conclusion: PCT and CRP levels were significantly higher in IPF-PNA group than in IPF-AE group. Compared with CRP, PCT was found to be a more sensitive biomarker in differentiating IPF-PNA from IPF-AE.

Keywords: Differential diagnosis, idiopathic pulmonary fibrosis, exacerbation, pneumonia, procalcitonin

ÖZ

Amaç: İdiyopatik pulmoner fibrozis (İPF) tanılı olgularda, İPF akut alevlenmesi (İPF-AA) ile pnömoninin (İPF-pnömoni) ayrımını yapmak genellikle zordur. Procalcitonin (PKT) bakteriyel pnömoniler için oldukça spesifik bir biyobelirteçtir. Bu çalışmada PKT'nin İPF-AA ile İPF-pnömoni ayrımındaki tanısal değeri araştırılmıştır.

Gereç ve Yöntemler: Ocak 2015 ile Haziran 2018 tarihleri arasında İPF-AA ve İPF-pnömoni tanıları ile hastaneye yatırılan olgular çalışmaya alınmış; demografik özellikleri, C-reaktif protein (CRP) ve PKT seviyeleri ile hastane yatış süreleri kaydedilmiştir.

Bulgular: Toplam 44 uygun hasta 1:1 oranında iki gruba randomize edilmiştir. PKT ve CRP seviyeleri İPF-pnömoni grubunda İPF-AA grubuna göre anlamlı olarak daha yüksek saptandı (PKT için 1.727±3.549 ng/mL'ye karşılık 0.642±0.049 ng/mL, p<0.001, ve CRP için 148.4±97.7 mg/L'ye karşılık 55.4±47.2 mg/L, p<0.001). Hastane yatış süresi İPF-pnömoni grubunda anlamlı olarak daha uzundu (15.18±8.3 gün'e karşılık 8.54±2.5 gün, p=0.001). Ayrıca, PKT için 0.1065 ng/mL eşik değer kabul edildiğinde, sensitivite, spesifisite,

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ÖZ

pozitif prediktif değer (PPD) ve negatif prediktif değer (NPD) sırası ile 0.955, 0.773, 0.808 ve 0.944 saptandı. CRP için eşik değer 35 mg/L olarak kabul edildiğinde ise sensitivite, spesifisite, PPD ve NPD sırası ile 0.955, 0.500, 0.656 ve 0.917 idi.

Sonuç: PKT ve CRP düzeyleri İPF-pnömoni grubunda İPF-AA grubuna göre anlamlı olarak yüksek saptandı. CRP ile karşılaştırıldığında PKT'nin, İPF-AA ile İPF-pnömoniyi ayırmada daha sensitif bir biyobelirteç olduğu gözlendi.

Anahtar Kelimeler: Ayırıcı tanı, idiyopatik pulmoner fibrozis, alevlenme, pnömoni, prokalsitonin

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease with a poor prognosis which is frequently diagnosed in older ages (1). Patients with IPF may experience sudden onset respiratory worsening, most of which is idiopathic and defined as acute exacerbation of IPF (IPF-AE). It is usually challenging to differentiate IPF-AE from heart failure, bilateral pneumonia (PNA), or pulmonary embolism (2). Cough, increased expectoration, dyspnea, hypoxemia, and newly formed parenchymal infiltrations on chest imaging are non-specific for IPF-AE; moreover, these observations can also be seen in bacterial PNA (3). Procalcitonin (PCT), the precursor of calcitonin, is produced by neuroendocrine cells when confronted with microbial toxins and inflammatory mediators. It is a highly specific biomarker for severe bacterial infections in suspected cases of sepsis (4,5). The objective of the study was to investigate the diagnostic value of PCT in the differential diagnosis of acute exacerbation and pneumonia in IPF patients.

Material and Methods

The data of IPF inpatients were retrospectively analyzed at a tertiary referral hospital between January 2015 and June 2018. Age, gender, presenting symptoms, duration of hospitalization, vital signs, biochemical markers [including C-reactive protein (CRP) and PCT levels], and radiological findings were recorded. Patients with incomplete data such as absence of thorax computerized tomography/high-resolution computerized tomography (CT/HRCT) and those who were hospitalized for other conditions such as pulmonary embolism, decompensated heart failure, pneumothorax, and acute renal failure were excluded from the study. Since the study was retrospective, patient consent was not obtained.

The diagnosis of IPF-AE was made according to the criteria suggested by the ATS/ERS/JRS/ALAT committee and the International Working Group Report by Collard et al. (6,7). The presence of fever (>37.5 °C), pneumonic consolidation in thoracic imaging, and positive sputum and/or blood culture were suggestive of PNA. On the other hand, if the patients had progressive dyspnea in the previous month, recently developed bilateral ground-glass opacities, and/or consolidations with a usual interstitial PNA pattern without heart failure or fluid retention, the diagnosis was IPF-AE (7).

CRP and PCT levels were measured using an immunoturbidimetric assay via Beckman Coulter AU Analyzer (US).

Study approval was taken from the Karabük University Ethics Committee on 03.01.2018 with verdict number 1/2.

Power Analysis

In the a priori power (G*Power Version 3.0) analysis in independent groups based on the data (effect size d=0.926, α=0.05, power=0.80) of a study by Ding et al. (8) on procalcitonin-guided antibiotic use in IPF-AE, it was calculated that at least 16 independent control and 16 experimental subjects were required for a study investigating procalcitonin testing. Each group of this independent study consisted of 22 subjects.

Statistical Analysis

The minimum (min), maximum (max), and mean ± standard deviation (SD) was calculated for all variables. The SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL, USA) was used to analyze the data. Frequency and percentage for discrete data and mean ± SD for continuous data were used in descriptive statistics. Normally distributed continuous data were analyzed by the Kolmogorov-Smirnov test while all nominal data were analyzed by the chi-square test. Non-parametric distributions were compared with the Mann-Whitney U test, and mean values with parametric distribution between groups were analyzed with Student's t-test. Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off values of the PCT and CRP to predict PNA. A p-value <0.05 was considered as statistically significant.

Results

Fifty-seven IPF patients were evaluated; 13 of them were excluded due to pulmonary embolism (n=1), decompensated heart failure (n=3), absence of HRCT scans (n=3), and failure to obtain laboratory work-up (n=6). A total of 44 eligible

patients were randomized into two groups at a 1:1 ratio. The mean age was 62.9±7.6 years in the pneumonia in patients with IPF (IPF-PNA) group and 67.3±6.6 years in the IPF-AE, with a statistically significant difference (p=0.049). The number of male patients was significantly higher in the IPF-PNA group (p=0.007) than in the IPF-AE.

The PCT levels were significantly higher in the IPF-PNA group than in the IPF-AE [0.253 ng/mL (0.10-12) vs. 0.05 ng/mL (0-0.15), p<0.001]. Additionally, the CRP levels were significantly higher in the IPF-PNA group than in the IPF-AE [129 mg/L (33.6-413) vs. 37.9 mg/L (4-152), p<0.001] (Figure 1). Also, the hospital stay was significantly higher in the IPF-PNA group (15.18±8.3 days vs. 8.54±2.5 days, p=0.001). Demographical data and laboratory results are summarized in Table 1.

ROC analysis was performed for identification of the PCT and CRP cut-off values to predict PNA in worsening IPF (Figure 2). When 0.1065 ng/mL was taken as the cut-off for PCT, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.955, 0.773, 0.808, and 0.944, respectively. When 35 mg/L was taken as the cut-off for CRP, the results were 0.955, 0.500, 0.656, and 0.917, respectively (ROC graphic, Table 2).

Regarding sputum analyses, the causative pathogens identified in the IPF-PNA group were *Klebsiella pneumoniae* (n=3), *Pseudomonas aeruginosa* (n=1), and *Escherichia coli* (n=1).

Discussion

In our study, the PCT and CRP levels were significantly higher in the IPF-PNA group when compared with the IPF-AE group. Also, the IPF-PNA group had a longer hospital stay. When the cut-off values of the CRP and PCT levels were specified, PCT was found to be a more sensitive biomarker for differentiating between IPF-PNA and IPF-AE.

The fact that both IPF-PNA and IPF-AE groups have similar clinical, laboratory, and radiologic findings makes it difficult to decide on antibiotic use. The differentiation between patients who require antibiotic treatment and

Table 1. General characteristics of the IPF-PNA and IPF-AE study groups

Characteristics	IPF-AE (n=22)	IPF-PNA (n=22)	[a]p-value
Age, years	62.9±7.6	67.3±6.6	0.049
Female/male	10/12	2/20	0.007
PCT, ng/mL	0.0642±0.049	1.727±3.549	<0.001
CRP, mg/L	55.4±47.2	148.4±97.7	<0.001
ESR, mm/hr	48.7±28.8	64.8±24.6	0.157
NLR	6.08±4.5	9.56±7.9	0.110
PLR	21.93±19.8	38.06±48.6	0.054
WBC	11.83±3.57	14.0±6.38	0.051
Neut	72.4±18.3	74.3±22.2	0.764
Lymph	18.9±14.4	12.3±7.1	0.059
Eos	1.4±1.5	1.3±1.5	0.571
Plt.	279.7±101.1	284.0±30.5	0.904
Length of stay, day	8.54±2.5	15.18±8.3	0.001

[a]: Mann-Whitney U test, IPF: Idiopathic pulmonary fibrosis, IPF-PNA: Pneumonia in patients with IPF, IPF-AE: Acute exacerbation of IPF, PCT: Procalcitonin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, WBC: White blood cells, Neut: Neutrophil, Lymph: Lymphocyte, Eos: Eosinophil, Plt: Platelet

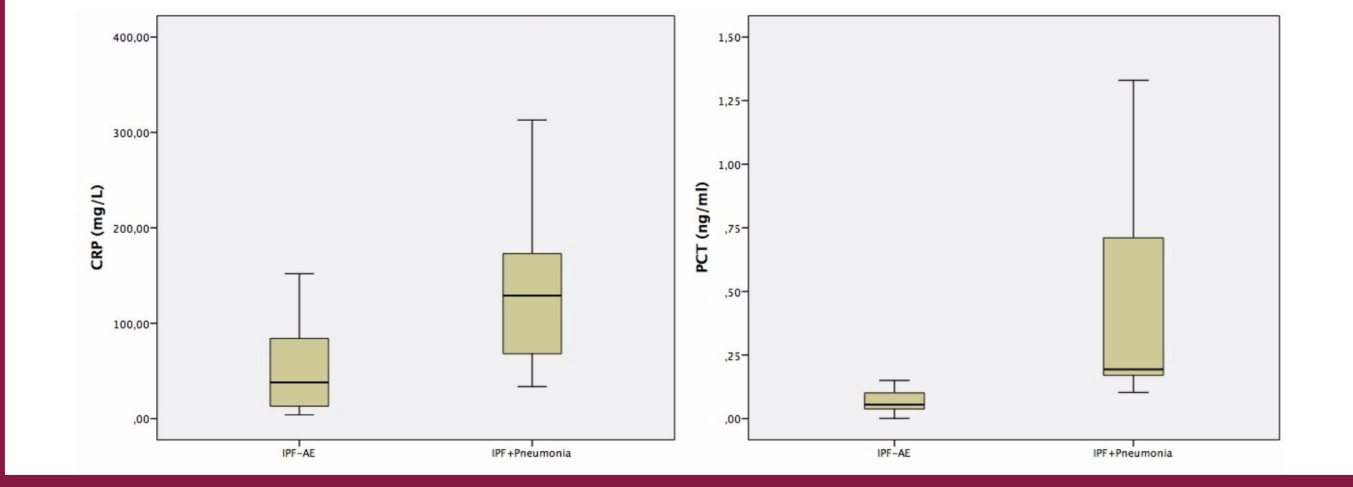

Figure 1. Distribution of PCT and CRP levels between study groups
PCT: Procalcitonin, CRP: C-reactive protein, IPF-AE: Acute exacerbation of IPF, IPF: Idiopathic pulmonary fibrosis

those who do not remains a challenge, as reliable clinical and/or microbiological parameters that are easily accessible during sampling are still inadequate. At this stage, the delayed availability of culture results, low sensitivities of some tests, and the contamination risk, especially in sputum cultures, pose challenges in making decisions regarding antibiotic usage. Inflammatory markers like CRP or white blood cells (WBC) are faster and more easily accessible indicators for indicating infection in daily practice, yet lack specificity for bacterial infections. This scenario has prompted the exploration of new biomarkers that are more discriminative. One of these biomarkers mentioned is PCT.

Procalcitonin is produced by the medullary C glands of the thyroid and neuroendocrine cells of the lung in the healthy population (9,10). It is a member of the CAPA protein family and is a 116 amino acid polypeptide (11). It rapidly converts into the 32 amino acid hormone calcitonin, which plays an important role in calcium hemostasis, and therefore presents in very small amounts in circulation (<0.01 ng/mL) (12). Depending on the type and severity of infection, varying amounts of PCT are released into the circulation from other parenchymal tissues and differentiated cell types (13,14). PCT serum levels are increased in bacterial, fungal, and parasitic infections, but do not rise or slightly increase during viral infections and non-infectious inflammatory reactions (14). It is also critical to differentiate between infectious and non-infectious exacerbations in IPF patients because bacterial PNA stands as a well-known leading cause of mortality in patients with IPF (7,15). Additionally, the treatments for these two conditions are very different from each other; while antibiotherapy is required for infectious exacerbations, systemic glucocorticoids are suggested for non-infectious exacerbations (16). Ding et al. (8) showed that PCT-guided antibiotic use in IPF-AE reduced antibiotic exposure and duration of antibiotic treatment, indicating that PCT is a useful biomarker in the management of these patients. In the light of this information, PCT, which gives quick result and provides practical approach, was preferred in our study design. The outcomes of our study also demonstrate that PCT can be employed as a biomarker to differentiate between IPF-AE and IPF-PNA.

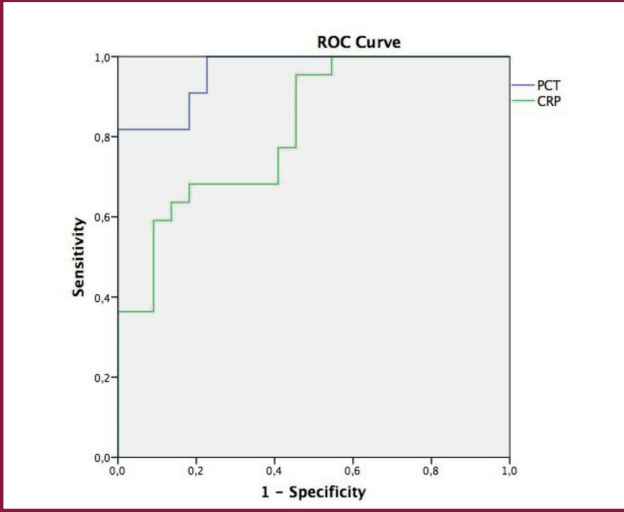

Figure 2. ROC curve for defining the PCT and CRP cut-off point predicting pneumonia

PCT: Procalcitonin, CRP: C-reactive protein, ROC: Receiver operating characteristic

Procalcitonin emerges as a more specific biomarker for the identification of bacterial infections. PCT is produced in response to endotoxins or bacterial infections, triggered by cytokines like interleukin (IL)-1b, tumor necrosis factor (TNF)-a, and IL-6 (17). The elevation of PCT levels is attenuated by interferon (INF)-ɣ released in viral infections, rendering it lower in viral infections and more specific for bacterial infections, allowing for the differentiation between bacterial and viral illnesses. A meta-analysis performed by Simon et al. (18) showed that PCT is more sensitive and specific than CRP for the differential diagnosis of viral and bacterial infection. It also helps in planning to start or cease antibiotic treatments (19). Because unnecessary and prolonged use of antibiotics increases antibiotic resistance and the risk of fungal infections (20,21). The widespread use of antibiotics is also a public health issue due to increased healthcare costs (22). However, avoiding antibiotics when PNA is suspected, is as dangerous as the overuse of antibiotics (23,24). The role of PCT has been researched in many different infectious diseases. ProHOSP study has shown that using PCT may reduce antibiotic use in emergency departments in infections of lower respiratory tract such as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbations of chronic obstructive pulmonary disease (25). Jain et al. (26) have illustrated

Table 2. Diagnostic accuracy rates of PCT and CRP in the differential diagnosis of IPF-PNA and IPF-AE study groups

	Cut-off	AUC	95% CI	Sensitivity/specifity	PPV	NPV	NLR	Accuracy	p-value
PCT, ng/mL	0.1065*	0.963	95% CI: 0.916-1.000	0.955/0.773	0.808	0.944	0.05	0.863	<0.001
CRP, mg/L	35**	0.820	95% CI: 0.699-0.942	0.955/0.500	0.656	0.917	0.09	0.727	<0.001

IPF: Idiopathic pulmonary fibrosis, IPF-PNA: pneumonia in patients with IPF, IPF-AE: Acute exacerbation of IPF, AUC: The area under the ROC curve, PPV: Positive predictive value, NPV: Negative predictive value, NLR: Negative likelihood ratio, PCT: Procalcitonin, CRP: C-reactive protein, *: ng/mL, **: mg/L

that PCT may be helpful in antibiotic decision-making for CAP. Moisa et al. (27) evaluated hematological biomarkers in distinguishing viral and bacterial sepsis and found that PCT was the best discriminative parameter among all measured parameters. Another retrospective study showed that PCT and CRP levels in non-neutropenic lung cancer patients with tumor fever to differentiate localized bacterial infection from bacteremia, and compared with CRP, PCT was to be more accurate in differentiating tumor fever from bacterial infections (28). Wang et al. (29) found that PCT was a more useful biomarker than CRP to differentiate acute radiation pneumonitis from bacterial PNA in patients with lung cancer. In a study examining WBC, CRP, and PCT levels of patients with cryptogenic organizing pneumonia (COP), another interstitial lung disease, were compared with CAP patients; PCT was shown to be a more useful biomarker in differentiating COP from CAP (30). In our study, which aimed to differentiate pneumonia from exacerbation according to inflammatory biomarkers measured on the first day of hospitalization, PCT was found to be more sensitive than CRP in predicting exacerbation in patients with IPF, which is consistent with the literature.

A systematic review assessing PCT's role as a predictor of sepsis has indicated that surpassing threshold levels in PCT could be a superior indicator compared to CRP. Nonetheless, it's noted that the cut-off values for patients can vary due to diverse surgical procedures, medication use, and immune system conditions (31). Ding et al. (8) have evaluated the feasibility of PCT in navigating antibiotic use in IPF-AE. One group of patients with IPF-AE was given antibiotics according to daily routine practice, whereas the other group was treated with the guidance of PCT levels. This study concluded that the use of 0.25 ng/mL as a threshold level for PCT decreased the length of antibiotic treatment and the number of patients receiving antibiotics (8). Sim et al. (3) have retrospectively evaluated 21 cases with interstitial lung disease who had recently increased dyspnea and worsened radiological findings. In nine of 21 patients, the cause of deterioration was bacterial PNA. They concluded that a cut-off value of 0.1 ng/mL for PCT may clearly indicate IPF-AE and facilitate clinical decision-making. At this threshold, the sensitivity, specificity, and NPV of serum PCT level are 88.9%, 100.0%, and 92.3%, respectively (3). In our study, when 0.1065 ng/mL was taken as the cut-off for PCT, the results were 95.5%, 77.3%, and 94.4%, respectively. Our findings are consistent with the previous study. Further large-scale studies are still needed to identify the exact cut-off values in more homogenous patient populations.

IPF is more common in older adult men and Kärkkäinen et al. (32) have reported that this is a risk factor for mortality in IPF-PNA patients. As far as we know, there is no data regarding the higher frequency of IPF-PNA cases in males compared to IPF-AE cases. A statistically significant predominance of male-sex in the IPF-PNA group was seen in this study.

Study Limitations

The limitations of the study can be described as the retrospective structure and the small sample size. Given the retrospective nature of our study, decisions regarding antibiotic initiation and cessation were not solely based on PCT. In order to comprehensively understand the role of this biomarker in guiding the clinical decision-making process, prospective studies are imperative. Additionally, it's noteworthy that most patients received PNA diagnoses through multidisciplinary evaluations and clinical and radiological assessments. Although this approach proves satisfactory in diagnosis, the absence of comprehensive microbiological confirmation constitutes another limitation of our study.

Conclusion

PCT and CRP levels were higher in the IPF-PNA than in the IPF-AE. Compared with CRP, PCT was found to be a more sensitive biomarker in differentiating IPF-PNA from IPF-AE. Future studies with larger study populations are essential on this issue.

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Ethics

Ethics Committee Approval: Study approval was taken from the Karabük University Ethics Committee on 03.01.2018 with verdict number 1/2.

Informed Consent: Since the study was retrospective, patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D., E.T., B.Z.Y., D.D., E.G.U.C., D.T., H.Ç., E.Ç., Concept: B.D., E.T., B.Z.Y., D.D., D.T., F.E.G., H.Ç., E.Ç., Design: B.D., E.T., B.Z.Y., D.D., E.G.U.C., F.E.G., H.Ç., E.Ç., Data Collection or Processing: B.D., E.G.U.C., D.T., F.E.G., Analysis or Interpretation: B.D., E.T., B.Z.Y., D.D., E.G.U.C., D.T., F.E.G., E.Ç., Literature Search: B.D., E.T., E.G.U.C., D.T., F.E.G., H.Ç., Writing: B.D., E.T., B.Z.Y., D.D., H.Ç., E.Ç.

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References

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205:18-47. [Crossref]
2. Luppi F, Cerri S, Taddei S, Ferrara G, Cottin V. Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. Intern Emerg Med. 2015;10:401-411. [Crossref]
3. Sim JK, Oh JY, Lee EJ, Hur GY, Lee SH, Lee SY, et al. Serum procalsitonin for differential diagnosis of acute exacerbation and bacterial pneumonia in patients with interstitial lung disease. Am J Med Sci. 2016;351:499-505. [Crossref]
4. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalsitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375:463-474. [Crossref]
5. Erenler AK, Yapar D, Terzi Ö. Comparison of Procalcitonin and C-reactive Protein in Differential Diagnosis of Sepsis and Severe Sepsis in Emergency Department. Dicle Medical Journal. 2017;44:175-182. [Crossref]
6. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:44-68. [Crossref]
7. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med. 2016;194:265-275. [Crossref]
8. Ding J, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. Int J Med Sci. 2013;10:903-907. [Crossref]
9. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89:1512-1525. [Crossref]
10. Han X, Zhong H, Hong D, Li C, Su H, Xu K. Elevated procalcitonin levels in primary hepatic neuroendocrine carcinoma: Case report and literature review. Medicine (Baltimore) 2020;99:e21210. [Crossref]
11. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med. 2008;36:941-952. [Crossref]
12. Irwin AD, Carrol ED. Procalcitonin. Arch Dis Child Educ Pract Ed. 2011;96:228-233. [Crossref]
13. Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J. 2007;30:556-573. [Crossref]
14. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. Intensive Care Med. 2000;26:1193-1200. [Crossref]
15. Shaddock EJ. How and when to use common biomarkers in community-acquired pneumonia. Pneumonia (Nathan). 2016;8:17. [Crossref]
16. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824. [Crossref]
17. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. J Infect Dis. 2000;181:176-180. [Crossref]
18. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39:206-217. [Crossref]
19. Jiang R, Han B, Dou C, Zhou F, Cao B, Li X. Analysis of antibiotic usage for viral community-acquired pneumonia in adults. Front Med. 2021;15:139-143. [Crossref]
20. Antoniou KM, Cottin V. The challenge of acute exacerbation of pulmonary fibrosis. Respiration. 2012;83:13-16. [Crossref]
21. Juarez MM, Chan AL, Norris AG, Morrissey BM, Albertson TE. Acute exacerbation of idiopathic pulmonary fibrosis-a review of current and novel pharmacotherapies. J Thorac Dis. 2015;7:499-519. [Crossref]
22. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CCH, Doi Y, et al. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. N Engl J Med. 2018;379:236-249. [Crossref]
23. Alyacoubi S, Abuowda Y, Albarqouni L, Böttcher B, Elessi K. Inpatient management of community-acquired pneumonia at the European Gaza Hospital: a clinical audit. Lancet. 2018;391(Suppl 2):40. [Crossref]
24. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med. 2004;164:637-644. [Crossref]
25. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Serv Res. 2007;7:102. [Crossref]
26. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415-427. [Crossref]
27. Moisa E, Dutu M, Corneci D, Grintescu IM, Negoita S. Hematological Parameters and Procalcitonin as Discriminants between Bacterial Pneumonia-Induced Sepsis and Viral Sepsis Secondary to COVID-19: A Retrospective Single-Center Analysis. Int J Mol Sci. 2023;24:5146. [Crossref]
28. Zhao Z, Li X, Zhao Y, Wang D, Li Y, Liu L, et al. Role of C-reactive protein and procalcitonin in discriminating between infectious fever and tumor fever in non-neutropenic lung cancer patients. Medicine (Baltimore). 2018;97:e11930. [Crossref]
29. Wang Z, Huo B, Wu Q, Dong L, Fu H, Wang S, et al. The role of procalcitonin in differential diagnosis between acute radiation pneumonitis and bacterial pneumonia in lung cancer patients receiving thoracic radiotherapy. Sci Rep. 2020;10:2941. [Crossref]
30. Ito A, Ishida T, Tachibana H, Arita M, Yamazaki A, Washio Y. Utility of procalcitonin for differentiating cryptogenic organising pneumonia from community-acquired pneumonia. Clin Chem Lab Med. 2019;57:1632-1637. [Crossref]
31. Hassan J, Khan S, Zahra R, Razaq A, Zain A, Razaq L, et al. Role of Procalcitonin and C-reactive Protein as Predictors of Sepsis and in Managing Sepsis in Postoperative Patients: A Systematic Review. Cureus. 2022;14:e31067. [Crossref]
32. Kärkkäinen M, Nurmi H, Kettunen HP, Selander T, Purokivi M, Kaarteenaho R. Underlying and immediate causes of death in patients with idiopathic pulmonary fibrosis. BMC Pulm Med. 2018;18:69. [Crossref]

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Postoperative Outcomes of V-notes (Transvaginal Natural Orifice Transluminal Endoscopic Surgery) Sacrocolpopexy in Patients with Pelvic Organ Prolapse

Pelvik Organ Prolapsusu Olan Hastalarda V-notes (Transvaginal Natural Orifice Transluminal Endoscopic Surgery) Sakrokolpopeksinin Postoperatif Sonuçları

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ABSTRACT

Background: This study introduces and evaluates a novel surgical approach for treating pelvic organ prolapse (POP) by combining vaginal natural orifice transluminal endoscopic surgery (V-NOTES) with sacrocolpopexy. The aim was to provide maximal benefit to patients through this approach, eliminating the need for additional incisions and utilizing the anterior longitudinal ligament for suspension.

Materials and Methods: The study enrolled 11 patients who underwent V-NOTES sacrocolpopexy after vaginal hysterectomy. The patients' quality of life improved significantly after the procedure, as indicated by the pelvic floor impact questionnaire and pelvic floor distress inventory scores. The technique involved using helical titanium tacks to secure the mesh to the anterior longitudinal ligament, streamlining the procedure and standardizing mesh fixation.

Results: The median age of patients was 64 years. The median operative time for V-NOTES sacrocolpopexy was 150 minutes. There were no perioperative complications, and postoperative pain scores were minimal. Patients expressed high satisfaction with cosmetic outcomes, and physical examination findings demonstrated significant improvement in POP.

Conclusion: V-NOTES sacrocolpopexy is an effective and promising approach for managing POP prolapse after vaginal hysterectomy. The procedure demonstrated positive outcomes in terms of operative time, complications, pain scores, cosmetic results, and hospital stay. Moreover, it significantly improved patients' quality of life, positively impacting daily activities and emotional well-being. As the incidence of POP is expected to rise with an aging population, V-NOTES sacrocolpopexy may offer a minimally invasive alternative for treating apical compartment prolapse.

Keywords: Pelvic organ prolapse, V-NOTES sacrocolpopexy, minimally invasive surgery, quality of life, anterior longitudinal ligament

ÖZ

Amaç: Bu çalışma, vajinal histerektomi sonrası pelvik organ sarkmasının (POP) tedavisi için vajinal doğal açıklık translüminal endoskopik cerrahi (V-NOTES) yönteminin sakrokolpopeksi ile birleştirilerek yeni bir cerrahi yaklaşımın tanıtılmasını ve değerlendirilmesini içermektedir. Amaç, bu yaklaşım aracılığıyla hastalara yapılacak ek insizyon ihtiyacını ortadan kaldırarak ve anterior longitudinal ligaman kullanarak maksimum fayda sağlamaktır.

Gereç ve Yöntemler: Çalışmaya vajinal histerektomi sonrası V-NOTES sakrokolpopeksi yapılan 11 hasta dahil edildi. Hastaların yaşam kalitesi, pelvik taban etki anketi ve pelvik taban rahatsızlık envanteri puanlarıyla değerlendirildi ve işlem sonrası önemli ölçüde iyileşme gösterdi. Teknikte, helikal titanyum çiviler kullanılarak meş anterior longitudinal ligamana sabitlendi. Bu teknik operasyonun kolaylaşmasının yanı sıra meş sabitlemesinin de standart hale gelmesini sağladı.

Bulgular: Hastaların ortanca yaşı 64'tü. V-NOTES sakrokolpopeksi için ortalama ameliyat süresi 150 dakikaydı. Perioperatif komplikasyonlar görülmedi ve ameliyat sonrası ağrı puanları minimaldi. Hastalar kozmetik sonuçlardan memnuniyetlerini yüksek düzeyde ifade ettiler ve fiziksel muayene bulguları POP'de önemli bir iyileşmeyi gösterdi.

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ÖZ

Sonuç: V-NOTES sakrokolpopeksi, vajinal histerektomi sonrası POP'yi yönetmek için etkili ve umut verici bir yaklaşımdır. İşlem, operasyon süresi, komplikasyonlar, ağrı skorları, kozmetik sonuçlar ve hastanede kalış süresi açısından olumlu sonuçlar göstermiştir. Ayrıca, hastaların yaşam kalitesini önemli ölçüde artırmıştır ve günlük aktivitelere ve duygusal iyilik haline olumlu etki etmiştir. POP insidansının yaşlanan nüfusla birlikte artması beklenirken, V-NOTES sakrokolpopeksi tedavide potansiyel faydalar sunan minimal invaziv bir alternatif olabilir.

Anahtar Kelimeler: Pelvik organ prolapsusu, V-NOTES sakrokolpopeksi, minimal invazif cerrahi, yaşam kalitesi, anterior longitudinal ligament

Introduction

The prevalence of pelvic organ prolapse (POP) varies between studies. It can occur at any age, yet studies have shown that POP symptoms peak between the ages of 70 and 79 (1). POP is expected to become more common as populations age (2). Therefore, gynecologists will be more likely to encounter patients with POP during routine examinations. However, even if it has been medically diagnosed, POP does not necessarily need to be treated unless the patient has complaints that affect quality of life. When patients present with POP symptoms, treatment options can be considered based on the type of prolapsed organ(s) and the severity of the condition.

Various vaginal or abdominal approaches have so far been described for the surgical treatment of POP (3). Suspension of the prolapsed vagina after hysterectomy is one of the surgical options in patients with total prolapse if no desire for fertility. Vaginal hysterectomy, which is considered the gold standard, can be performed in patients with POP without the need for abdominal incision. After hysterectomy, ligaments such as the sacrospinous ligament, iliopectineal ligament or anterior longitudinal ligament may be preferred to suspend a prolapsed vagina (4). The anterior longitudinal ligament was determined as the ligament with the highest tensile strength among the pelvic ligaments (5). Many consider sacrocolpopexy, where the vagina is suspended to the anterior longitudinal ligament, to be top choice for treating apical compartment prolapse. In order to perform sacrocolpopexy surgery, the anterior longitudinal ligament must be exposed by dissecting the peritoneum over the sacrum. However, there is a problem of inadequate exploration to safely perform sacrocolpopexy through vaginal route. Therefore, hysterectomy with abdominal or laparoscopic approach is generally preferred in patients who will undergo sacrocolpopexy surgery. With the widely recognized benefits of minimally invasive procedures, like quicker recovery, reduced hospitalization time, and diminished pain, it's quite understandable that surgeons would lean towards laparoscopic sacrocolpopexy over abdominal sacrocolpopexy whenever feasible. However, an abdominal incision is required to perform sacrocolpopexy in conventional and single-port abdominal laparoscopic surgery.

Transvaginal natural orifice transluminal endoscopic surgery (V-NOTES), which can be defined as single port laparoscopic surgery through the vaginal route, has started to gain popularity in recent years. Apart from the vaginal incision, which has to be made regardless of the surgical approach, the absence of the need for an additional incision in V-NOTES hysterectomy and subsequent surgical procedures that can be performed vaginally is one of the important aspects that distinguishes V-NOTES from other laparoscopic surgeries. Moreover, V-NOTES allows exploration of the entire abdominal cavity via using the vaginal route only. Thus, the exploration required to safely perform sacrocolpopexy, which is the gold standard method, can be achieved with V-NOTES.

In this study, we combined the main elements of two gold standard methods by completing the operation without making an additional incision and using the strongest pelvic ligament in suspension. We aimed to provide maximum benefit to patients by performing V-NOTES sacrocolpopexy after vaginal hysterectomy. We reported the perioperative and early postoperative results of V-NOTES sacrocolpopexy in patients with POP and its effect on patients' quality of life.

Material and Methods

The study enrolled individuals who visited the obstetrics and gynecology outpatient clinic due to POP concerns and underwent V-NOTES sacrocolpopexy. The University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee granted ethical approval for the study (reference number: 2022/514/222/30). Specifically, those aged 45 to 79, exhibiting stage III or IV prolapse according to POP-Q classification, free from contraindications for pneumoperitoneum and the Trendelenburg position, and suitable for transvaginal NOTES were included. Preoperatively, two surgeons conducted evaluations for all patients. All patients were operated by the same surgeons. In the assessment of patients for contraindications to

the Trendelenburg position and pneumoperitoneum, the anesthesiologist conducted a comprehensive evaluation. This evaluation involved a thorough review of the patient's medical history, including any preexisting cardiovascular, respiratory, or neurological conditions. Additionally, the anesthesiologist performed a physical examination to assess factors such as hemodynamic stability, lung function, and neurological status. Special attention was given to identifying any potential contraindications, such as severe cardiac disease, intracranial hypertension, or compromised respiratory function. The goal of this meticulous evaluation was to ensure patient safety and make informed decisions regarding the feasibility of utilizing the Trendelenburg position and pneumoperitoneum during surgical procedures.

Information regarding demographics, age, medical and surgical background body mass index (BMI), surgical duration, pre- and post-operative hemoglobin levels, perioperative complications, and hospitalization duration were gathered. The surgical duration was measured from the initial incision to the final suture. Intraoperative complications encompassed ureteral, bladder, bowel, and vascular injuries. Hematoma, infection, pain, mesh erosion, ileus and new onset urinary incontinence were considered as postoperative complications. The patients were evaluated with visual analogue scale (VAS) at the postoperative 24th hour, with a pain score of 0 (no pain) to 10 (worst pain). In the 1st month after the operation, cosmetic scoring was performed using the VAS scale, as 1 (not at all satisfied) 10 (very satisfied).

Both before and one month after surgery, the POP quantification (POP-Q) scores were assessed. The Turkish-validated pelvic floor impact questionnaire (PFIQ-7) and pelvic floor distress inventory (PFDI-20) were used to assess quality of life before and one month after the surgery. The PFIQ-7 is an assessment form that questions the impact of pelvic floor function on daily activities, quality of life, and emotional health. Comprising a total of 21 questions categorized into three subgroups- the urinary impact questionnaire (UIQ), the colorectal-anal impact questionnaire (CRAIQ) and the pelvic organ prolapse impact questionnaire (POPIQ)- the PFIQ-7 was employed. The higher the score on the PFIQ-7, the greater the impact of pelvic floor dysfunction on the patient's life. PFDI-20 is an assessment form that aims to evaluate the level of discomfort associated with symptoms. The PFDI-20 consist of 3 scales: Pelvic organ prolapse distress inventory (POPDI), urinary distress inventory (UDI) and colorectal-anal distress inventory (CRADI). According to the degree of their complaints, patients answer a total of 20 questions as 0 (absent), unimportant (1), little (2), moderate (3), a lot (4). A maximum of 300 points can be scored. The higher the score, the greater the pelvic floor dysfunction.

Surgical Technique

A single dose of 2 g of cefazolin IV was administered. The procedure was carried out with the use of general anesthesia. After holding the cervix with a tenaculum, a circular incision was made around the cervix. In the posterior part of the circular incision, the vaginal wall was held with Allis clamps. After the peritoneum was identified, it was cut with scissors. Then, the anterior vaginal wall was held with Allis clamps. Vesicouterine pouch was entered by sharp dissection while protecting the bladder. Retractors were utilized to protect bladder and rectum. The uterosacral and cardinal ligament complex, uterine vessels, broad ligament, utero-ovarian ligament, round ligament and cornual end of the Fallopian tube were sealed and cut, with a vessel sealing system (LigaSure™, Medtronic, Mansfield, MA). Thus, the uterus was freed from all attachments and the hysterectomy was completed. The polypropylene mesh (POLYMESH Polypropylene, Betatech Medical Devices ABD drugs, Türkiye) was then placed on the posterior part of the vaginal cuff with 2-0 non-absorbable monofilament polypropylene suture. The GelPOINT advanced access platform (Applied Medical Resources Corp., Rancho Santa Margarita) was used for V-NOTES. First, a wound retractor (Alexis O wound protector-retractor; Applied Medical Resources Corp., Rancho Santa Margarita) was inserted through vagina into the abdominal cavity. The GelSeal cap with 4 low-profile sleeves (Applied Medical Resources Corp., Rancho Santa Margarita) was placed over the wound retractor. CO_2 was insufflated through this port to a pressure of 12 mmHg at a flow rate of 0.4 L/min. The adnexa were grasped with a laparoscopic grasper. The infundibulopelvic ligament was sealed and cut with a vessel sealing system. Bilateral adnexectomy was performed. The operating table was tilted to 30° of Trendelenburg position so that the sacral promontorium could be seen. Then, the intestines were retracted with a fan-shaped retractor (Karl Storz GmbH and Company, Tuttlingen, Germany). The peritoneum covering the sacral promontory was ligated, incised, and divided using a vessel sealing system (LigaSure™, Medtronic, Mansfield, MA. The anterior longitudinal ligament was revealed. Ureteral course identified. The mesh was fastened to the anterior longitudinal ligament using helical titanium tacks (ProTack™, Medtronic, Mansfield, MA, USA). The GelPOINT advanced access platform was removed. The Vaginal cuff was sutured shut using a continuous and locking technique with delayed absorbable polyglactin 910 suture (Vicryl®, Ethicon Inc., Somerville, NJ, USA).

Statistical Analysis

The statistical analysis was conducted using SPSS version 25 (IBM; Chicago, IL, USA). The analysis includes frequency and percentage figures for qualitative variables, along with median, minimum and maximum values for quantitative variables. The Wilcoxon test was used for comparison of repeated measurements before and after surgery. Type I error rate was taken as α=0.05 in the study.

Results

Thirteen patients who fulfilled the eligibility criteria and provided written informed consent underwent V-NOTES sacrocolpopexy. Despite two patients expressing satisfaction with the surgery during a telephone interview, they did not attend the clinic for a physical examination within the initial month following the operation. The study comprised the remaining eleven patients. The median age of the patients was 64 (range, 55-77) years. Among the patients six had hypertension four had diabetes mellitus, and three had coronary artery disease. Median BMI of the patients was 29 kg/m^2 (range, 20 - 34 kg/m^2). The median operation time was found to be 150 (range, 80-210) minutes. There were no perioperative complications. None of the cases were converted to laparoscopy or laparotomy. The median VAS score at the postoperative 24th hour was 0. The median preoperative hemoglobin level was 13 mg/dL (range, 11 to 14). The median postoperative hemoglobin level was 12.3 mg/dL (range, 10.4 to 13.6). The median hospital stay of the patients after the operation was 2 days. All patients had a cosmetic score of 10 in the first month postoperatively.

Before the surgery, all patients were classified as stage 3 or 4 according to the POP-Q staging system. In the physical examination of the patients at the 1st month postoperatively, it was found that all patients had POP-Q stage 0 or 1. In the preoperative phase, the median total score on the PFIQ-7 was 166. The median PFIQ-7 total score was 0 at the first postoperative month. When comparing the preoperative and postoperative median total scores on the PFIQ-7, a statistically significant difference was observed (p=0.003). This notable contrast underscores the surgery's favorable impact on patients' daily activities, quality of life, and emotional well-being. Subgroups of PFIQ-7 were also evaluated. A statistically significant difference was found between the pre- and postoperative periods in UIQ and POPIQ scores (p=0.008, p=0.003, respectively). There was no statistically significant difference in CRAIQ scores. The median PFDI-20 scores of the patients in the preoperative period was 37. The median PFDI-20 scores of the patients in the postoperative period were 0. There was a statistically significant difference between the preoperative and postoperative PFDI scores of the patients (p=0.003). When the subgroups of PFDI, namely POPDI, CRADI, and UDI, were examined separately, a statistically significant difference was found in each subgroup. The median, minimum and maximum values, p-values and Z scores of the patients' preoperative and postoperative PFDI-20 and PFIQ-7 evaluations are shown in Table 1.

Discussion

In this study, we introduced and evaluated a novel surgical approach for treating POP by combining V-NOTES with sacrocolpopexy. This approach involved performing V-NOTES sacrocolpopexy after vaginal hysterectomy, which not only eliminated the need for additional incisions but also harnessed the strength of the anterior longitudinal ligament for suspension. Our findings demonstrated favorable outcomes in terms of surgical success, reduced postoperative pain, and excellent cosmetic results. Patients reported improvements in quality of life. Moreover, the technique of using helical titanium tacks for mesh fixation expedited the procedure and enhanced standardization. This innovative approach holds promise for selected patients and provides a compelling alternative in the field of minimally invasive surgical treatments for POP. The combination of reduced surgical invasiveness, favorable clinical outcomes, and improved patient experience emphasizes the clinical implications of adopting this approach in suitable candidates for POP treatment.

Minimally invasive surgery aims for less surgical damage, less inflammation, and less neuroendocrine

Table 1. Pre- and postoperative pelvic floor distress inventory short form 20 and pelvic floor impact questionnaire short form 7 scores of the patients

	Preoperative	Postoperative	p-value
Total PFDI-20 score	37 (10-52)	0 (0-16)	0.003*
POPDI score	14 (4-24)	0 (0-2)	0.003*
CRADI score	5 (0-13)	0 (0-3)	0.007
UDI score	13 (5-23)	0 (0-16)	0.005
Total PFIQ-7 score	166 (75-246)	0 (0-100)	0.003*
CRAIQ score	0 (0-100)	0 (0-0)	0.068
UIQ score	28 (0-100)	0 (0-100)	0.008
POPIQ score	90 (66-100)	0 (0-0)	0.003*

PFDI-20: Pelvic floor distress inventory short form 20, POPDI: Pelvic organ prolapse distress inventory, CRADI: Colorectal-anal distress inventory, UDI: Urinary distress inventory, PFIQ-7: Pelvic Floor impact questionnaire short form 7, CRAIQ: Colorectal-anal impact questionnaire, UIQ: Urinary impact questionnaire, POPIQ: Pelvic organ prolapse impact questionnaire. Data are presented as median (min-max)

response, and thus less postoperative pain, rapid recovery, and good cosmetic results. In operations that can be performed vaginally after hysterectomy, completing the procedure through the vaginal incision without making any additional incision may contribute to these benefits. Therefore, it seems reasonable to perform sacrocolpopexy vaginally after vaginal hysterectomy. To date, only a few studies have reported laparoscopic or robotic V-NOTES sacrocolpopexy (6,7,8). When V-NOTES sacrocolpopexy is performed, laparoscopic suturing appears to prolong the operative time. On the other hand, robotic surgery is not available in many hospitals and increases the cost of surgery. These can be overcome by securing the mesh to the anterior longitudinal ligament using tacks in V-NOTES sacrocolpopexy. To the best of our knowledge, this is the first study to report the results of V-NOTES sacrocolpopexy with helical titanium tacks after vaginal hysterectomy.

The first reports of V-NOTES sacrocolpopexy were published in the literature about 4 years ago. Early publications consisted of case reports and technical details (6,8,9). This was followed by the publication of the early results of a series of 26 patients who underwent V-NOTES sacrocolpopexy by Liu et al. (7). In these studies, laparoscopic suturing was used to secure the mesh to the anterior longitudinal ligament. Based on the technically challenging nature of suturing/knotting in V-NOTES sacrocolpopexy, Guan et al. (8) published the first report on robot-assisted V-NOTES sacrocolpopexy. The literature shows that tacks or suturing can be used in the fixation of the mesh in sacrocolpopexy (9,10). Laparoscopic suturing requires training and knot security may vary depending on the technique and skill of the surgeon. On the other hand, tacks are easy to use and can standardize the mesh fixation step regardless of the surgeon's skill. In this study, we fixed the mesh to the anterior longitudinal ligament with helical titanium tacks. Thus, we both standardized the fixation of the mesh to the ligament and shortened the time of the laparoscopic part of the operation. In addition, in abdominal laparoscopic surgery, where the laparoscope is inserted through the abdomen, the sacrum can be viewed from above. Therefore, there may be difficulties in fixing the mesh to the anterior longitudinal ligament. However, in V-NOTES sacrocolpopexy, if the rectum is retracted laterally with an atraumatic grasper, the ventral side of the sacrum can be easily seen. Better visualization of the operative field can help fix the mesh in the correct anatomical position and shortens the operation time. Moreover, additional prolapse and/or urinary incontinence surgeries can be performed vaginally, if needed, without the need to change position after V-NOTES sacrocolpopexy. In our study, the median operation time was 150 minutes.

In our previous studies, we stated that especially obese patients could benefit from V-NOTES (11,12). Similarly, we believe the group that will benefit most from V-NOTES sacrocolpopexy will be obese patients. Obese patients may particularly benefit from V-NOTES sacrocolpopexy due to a combination of factors related to their anatomy and the advantages of the surgical technique. Obesity is associated with increased surgical risks, such as higher rates of surgical site infections and compromised respiratory function during laparoscopic procedures (13). V-NOTES sacrocolpopexy presents several attributes that can mitigate these risks in obese patients. Firstly, the absence of additional incisions in V-NOTES sacrocolpopexy after vaginal hysterectomy eliminates the potential complications associated with incisions, such as infection and incisional hernias, which are more prevalent in obese individuals. As adipose tissue is more susceptible to infections and wound healing complications, avoiding additional incisions is especially beneficial for obese patients (13).

Secondly, the shorter laparoscopic portion of the surgery in V-NOTES sacrocolpopexy compared to traditional laparoscopic approaches reduces the potential negative impact of pneumoperitoneum and the Trendelenburg position on respiratory function. Obesity is linked to decreased lung function, and these physiological challenges can be exacerbated by factors like intra-abdominal pressure changes and altered diaphragmatic mechanics during laparoscopy. V-NOTES sacrocolpopexy, with its shorter laparoscopic component, may reduce the overall impact on respiratory function and help prevent complications in obese patients.

Moreover, the standardized fixation of the mesh to the anterior longitudinal ligament using helical titanium tacks simplifies the surgical procedure, irrespective of the surgeon's experience. This reduces operative time, which is beneficial for obese patients who are at higher risk of complications with longer surgeries. Additionally, the improved visualization of the operative field in V-NOTES sacrocolpopexy facilitates accurate mesh placement, enhancing surgical outcomes for obese patients. Considering these factors, V-NOTES sacrocolpopexy's combination of certain advantages, including decreased incision-related complications, potentially limited impact on respiratory function, and standardized surgical steps, might be worth exploring for obese patients with pelvic organ prolapse. This approach not only addresses the specific challenges posed by obesity but also aligns with the overall goals of minimizing surgical invasiveness, optimizing patient outcomes, and improving quality of life. In the present study,

almost half of the patients (5 out of 11) had a BMI of 30.0 kg/m^2 or higher. The median laparoscopic surgery time for V-NOTES sacrocolpopexy was 20 minutes (range, 10 to 30). Adverse respiratory system events were not observed in any patient.

Li et al. (14) conducted a retrospective cohort study comparing V-NOTES sacrocolpopexy with multi-port laparoscopic sacrocolpopexy, revealing comparable perioperative outcomes in both methodologies. The main difference between the two groups in that study was that patients who underwent V-NOTES sacrocolpopexy had lower pain scores and higher cosmetic scores. As mentioned before, when V-NOTES sacrocolpopexy is performed after vaginal hysterectomy, there is no need for an additional incision other than the vaginal incision. Thus, there is no pain that may arise from an additional incision. The cosmetic results of the patients are excellent as there are no visible incisions in V-NOTES. In the current study, the median VAS score of the patients at the 24th hour was 0. The cosmetic score of all patients was 10 at postoperative 1st month.

Pelvic floor dysfunction can affect daily activities, emotional health and quality of life. There are various assessment forms to understand the impact of pelvic floor dysfunction. To understand the effect of treatment on pelvic floor dysfunction, these forms can be performed before and after treatment and the results can be compared. We performed pre- and postoperative PFDI-20 and PFIQ-7 evaluations on the patients. When the preoperative and postoperative median PFDI-20 and PFIQ-7 scores of the patients were compared, statistically significant difference was found (p=0.003 and p=0.003), respectively. A statistically significant difference was also found in all subgroup scores of the evaluations, except for the CRAIQ score. All patients had a CRAIQ score of 0 in the postoperative period. When the CRAIQ scores of the patients in the preoperative period were examined, it was seen that only 4 patients had scores other than 0. Therefore, the low preoperative scores were considered as a possible reason for not detecting a statistically significant difference in CRAIQ scores. Considering the physical examination findings, POP-Q evaluation of all patients was stage 4 in the preoperative period and 0 at postoperative 1st month.

Conclusion

V-NOTES sacrocolpopexy after vaginal hysterectomy is a remarkable method that can be preferred in well-selected patients, characterized by good results in both physical examination and self-reported pelvic floor function assessment. The surgery stands out with its high cosmetic scores and low pain scores. Utilizing tacks to secure the mesh to the anterior longitudinal ligament not only shortens the operative time but also standardizes the procedure, mitigating variations in surgical experience.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee granted ethical approval for the study (reference number: 2022/514/222/30).

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: E.C.G., E.B.Ö., Concept: E.C.G., E.B.Ö., Design: E.C.G., E.B.Ö., Data Collection or Processing: E.C.G., E.B.Ö., Analysis or Interpretation: E.C.G., E.B.Ö., Literature Search: E.C.G., E.B.Ö., Writing: E.C.G., E.B.Ö.

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References

1. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol. 2001;184:1496-1503. [Crossref]
2. Wu JM, Hundley AF, Fulton RG, Myers ER. Forecasting the prevalence of pelvic floor disorders in US women: 2010 to 2050. Obstet Gynecol. 2009;114:1278-1283. [Crossref]
3. Jones KA, Shepherd JP, Oliphant SS, Wang L, Bunker CH, Lowder JL. Trends in inpatient prolapse procedures in the United States, 1979-2006. Am J Obstet Gynecol. 2010;202:501. [Crossref]
4. Biler A, Ertas IE, Tosun G, Hortu I, Turkay U, Gultekin OE, et al. Perioperative complications and short-term outcomes of abdominal sacrocolpopexy, laparoscopic sacrocolpopexy, and laparoscopic pectopexy for apical prolapse. Int Braz J Urol. 2018;44:996-1004. [Crossref]
5. Cosson M, Boukerrou M, Lacaze S, Lambaudie E, Fasel J, Mesdagh H, et al. A study of pelvic ligament strength. Eur J Obstet Gynecol Reprod Biol. 2003;109:80-87. [Crossref]
6. Chen Y, Li J, Zhang Y, Hua K. Transvaginal single-port laparoscopy sacrocolpopexy. J Minim Invasive Gynecol. 2018;25:585-588. [Crossref]
7. Liu J, Kohn J, Fu H, Guan Z, Guan X. Transvaginal natural orifice transluminal endoscopic surgery for sacrocolpopexy: a pilot study of 26 cases. J Minim Invasive Gynecol. 2019;26:748-753. [Crossref]
8. Guan X, Guan Z, Koythong T, Liu J, Delgado S, Wang Q. Integration of a robotic platform for sacrocolpopexy in transvaginal natural orifice transluminal endoscopic surgery: a novel surgical technique. Urology. 2021;154:109-114. [Crossref]
9. Liu J, Kohn J, Sun B, Guan Z, Liang B, Guan X. Transvaginal Natural Orifice Transluminal Endoscopic Surgery Sacrocolpopexy: Tips and Tricks. J Minim Invasive Gynecol. 2019;26(Suppl):22. [Crossref]
10. Formijne Jonkers HA, van de Haar HJ, Draaisma WA, Heggelman BG, Consten EC, Broeders IA. The optimal strategy for proximal mesh fixation during laparoscopic ventral rectopexy for rectal prolapse: an ex vivo study. Surg Endosc. 2012;26:2208-2212. [Crossref]

11. Mat E, Kale A, Gundogdu EC, Basol G, Yildiz G, Usta T. Transvaginal natural orifice endoscopic surgery for extremely obese patients with early-stage endometrial cancer. J Obstet Gynaecol Res. 2021;47:262-269. [Crossref]
12. Kale A, Mat E, Başol G, Gündoğdu EC, Aboalhasan Y, Yildiz G, et al. A New and Alternative Route: Transvaginal Natural Orifice Transluminal Endoscopic Scarless Surgery (vaginal natural orifice transluminal endoscopic surgery) For Class 2 and Class 3 Obese Patients Suffering From Benign and Malignant Gynecologic Pathologies. Surg Innov. 2022;29:730-741. [Crossref]
13. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis. 2006;6:438-446. [Crossref]
14. Li J, Sima Y, Hu C, Wang X, Lu Z, Hua K, et al. Transvaginal single-port versus multi-port laparoscopic sacrocolpopexy: a retrospective cohort study. BMC Surg. 2022;22:82. [Crossref]

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Serratia spp. Infections Outside An Outbreak Scenario: A Five-year Review of Patients in A University Hospital

Salgın Senaryosunun Dışındaki *Serratia* spp. Enfeksiyonları: Bir Üniversite Hastanesindeki Hastaların Beş Yıllık Değerlendirmesi

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ABSTRACT

Background: *Serratia* spp. are Gram-negative bacilli commonly found in soil and water, causing opportunistic infections particularly in hospital settings.

Materials and Methods: A hospital review of patients hospitalized from 2017 to 2022 was made to identify patients whose clinical cultures grew *Serratia* spp. Inclusion criteria were age ≥18 years and isolation of one or more positive blood cultures for *Serratia* spp. Bacteremia was classified into two groups: Primary hospital-acquired bacteremia detected after 48 hours of hospitalization and bacteremia detected within the first 48 hours that was associated with previous healthcare facilities or applications.

Results: During the study period, *Serratia* spp. were identified in blood cultures of 46 patients (52.7% males; mean age 60.7±17.6 years). Thirty-one patients (67.4%) had hospital-acquired bacteremia, while 15 patients had bacteremia acquired from previous healthcare facilities or applications. Thirty-five patients (76.1%) were infected by *Serratia marcescens*. All patients had predisposing risk factors for bacteremia, the most common being malignancies (n=19), followed by cardiac diseases (n=16), and diabetes mellitus (n=13). A history of antibiotic treatment in the past month was common (67.4%). Compared with patients who acquired bacteremia from previous healthcare facilities or applications, the rate of prior antibiotic use was significantly higher in patients with hospital-acquired bacteremia (p<0.01), so was the rate of appropriate empirical antibiotic use (p=0.01). Resistance to piperacillin/tazobactam was significantly more common among patients who acquired bacteremia from previous healthcare facilities or applications (p=0.02). Resistance to carbapenem in this group was also higher than expected (20%). During hospitalization, sepsis developed in 27 patients (58.7%). Within 30 days after laboratory detection of *Serratia* spp., mortality occurred in 16 patients (34.8%).

Conclusion: The rate of healthcare-associated bacteremia is alarmingly high among hospitalized patients, which requires a meticulous inquiry into previous histories.

Keywords: *Serratia marcescens*, *Serratia* spp., healthcare-associated infection, bacteremia

ÖZ

Amaç: *Serratia* türleri toprakta ve suda yaygın olarak bulunan ve özellikle hastane ortamlarında fırsatçı enfeksiyonlara neden olan Gram-negatif basillerdir.

Gereç ve Yöntemler: Klinik kültürlerinde *Serratia* spp. üremesi olan hastaları belirlemek için 2017-2022 yılları arasında yatırılarak izlenen hastalar değerlendirmeye alındı. Dahil edilme kriterleri ≥18 yaş ve bir veya daha fazla kan kültüründe *Serratia* spp. üremesi olan hastalar olarak belirlendi. Hastaneye yattıktan 48 saat sonra saptanan primer hastane kaynaklı bakteriyemiler ve daha önceki sağlık kuruluşu başvuruları veya sağlık uygulamaları ile ilişkili olan ve ilk 48 saat içinde saptanan bakteriyemiler olmak üzere bakteriyemiler iki gruba ayrıldı.

Bulgular: Çalışma süresi boyunca, 46 hastanın (%52,7'si erkek; ortalama yaş 60,7±17,6) kan kültürlerinde *Serratia* spp. saptandı. Hastaların 31'inde (%67,4) hastane kaynaklı bakteriyemi, 15 hastada ise daha önceki sağlık kuruluşu başvuruları veya sağlık uygulamalarından kaynaklanan bakteriyemi vardı. Otuz beş hasta (%76,1) *Serratia marcescens* ile enfekteydi. Tüm hastalarda bakteriyemi için predispozan risk faktörleri vardı; en sık görülen risk faktörleri sırasıyla maligniteler (n=19), kalp hastalıkları

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ÖZ

(n=16) ve diyabet (n=13) idi. Son bir ayda antibiyotik tedavisi alma öyküsü yaygındı (%67,4). Hastane kökenli bakteriyemisi olan hastalarda önceki sağlık kuruluşu başvuruları veya sağlık uygulamaları kaynaklı bakteriyemisi olan hastalara kıyasla bakteriyemi öncesi antibiyotik kullanma oranı ve uygun ampirik antibiyotik kullanma oranı anlamlı derecede yüksekti (sırasıyla p<0,01, p=0,01). Piperasilin/tazobaktama direnç, önceki sağlık kuruluşu başvuruları veya sağlık uygulamaları kaynaklı bakteriyemisi olan hastalarda anlamlı olarak daha yüksekti (p=0,02). Bu grupta karbapenem direnci de beklenenden daha yüksekti (%20). Hastaneye yatış sırasında 27 hastada sepsis gelişti. *Serratia* spp.'nin laboratuvarda tespit edilmesinden sonraki 30 gün içinde 16 hastada (%34,8) ölüm meydana geldi.

Sonuç: Hastanede yatan hastalar arasında sağlık hizmetiyle ilişkili bakteriyemi oranı endişe verici derecede yüksektir ve bu da hastaların geçmiş öykülerin titiz bir şekilde araştırılmasını gerektirir.

Anahtar Kelimeler: *Serratia marcescens*, *Serratia* spp., sağlık hizmeti ilişkili enfeksiyon, bakteriyemi

Introduction

Serratia spp. are Gram-negative bacilli commonly found in soil and water (1,2). Although it had long been considered a nonpathogenic agent, *Serratia* spp. has now been recognized as an infectious agent since the 1970s and has been reported as a source of community- and hospital-acquired and even healthcare-associated infections (3,4). *Serratia* spp. accounts for 1-2% of all hospital-acquired infections in a wide variety of hospital settings, particularly in adult intensive care and neonatal intensive care units (ICU) (5,6). A large number of reports are about hospital outbreaks caused *by Serratia* spp. leading to bacteremia, urinary tract, respiratory tract and wound-site infections, endocarditis, and osteomyelitis which originate from use of central venous catheters and some medications (heparin, magnesium sulphate, propofol, etc.) as well as human sanitary neglect (7,8,9,10,11,12,13,14,15,16,17,18). There have also been individual case reports on *Serratia* spp.-associated endocarditis (19), meningitis (20,21), and soft-tissue infections (22,23). In addition, intrinsic or emerging resistance of *Serratia* spp. to commonly used beta-lactam antibiotics is a growing concern among healthcare professionals (5).

Due to the ubiquitous presence of the organism in the nature, some authors proposed to seek the actual source of *Serratia* bacteremia detected in primary hospital settings from those acquired from community or previous healthcare facilities or applications (7,24,25). Indeed, healthcare-associated infections other than acquired in a primary hospital setting are a growing problem worldwide, contributing to antibiotic resistance, and complicating establishment of appropriate antibiotic therapy as well as increasing morbidity and mortality (9,24). This makes this differentiation important when examining patient populations with respect to the actual source of infections and their appropriate treatment.

This study was designed to determine individual cases of *Serratia* spp. bacteremia in a tertiary health care center over a five-year period and to document laboratory and clinical characteristics of patients, with emphasis on the need for differentiation of bacteremia acquired in a primary hospital setting and that acquired from previous healthcare facilities or applications.

Material and Methods

A hospital review of patients hospitalized from February 2017 to 2022 was made to identify patients whose clinical cultures grew *Serratia* spp.. Our 900-bed university hospital includes six adult ICUs and newborn and pediatric ICUs. After a comprensive search from hospital electronic records and patient charts, patients were identified whose one or more blood cultures grew *Serratia* spp. and those who were 18 years of age or older were selected as eligible participants.

Exclusion criteria included patients whose clinical data were absent or missing and those with community-acquired bacteremia, as defined by the absence of a previous history of any healthcare service within the past 30 days despite positive cultures detected within the first 48 hours of hospitalization.

Patients with positive cultures for *Serratia* spp. were further analyzed with respect to socio-demographic characteristics, the length of hospitalization until detection of *Serratia* spp., diagnosis at admission, comorbidities, recent histories of admission, treatment and interventions prior to the current hospitalization, antibiotic treatments prior to and after the detection of *Serratia* spp. becteremia, and hospital setting at the time of growth of *Serratia* spp.. Blood samples were processed using the automated Phoenix™ system (Becton Dickinson Diagnostics, USA).

The study was approved by the institutional review board of Pamukkale University (04.01.2023/E.310937) and was conducted in accordance with the Declaration of Helsinki. Analysis and reporting of the results are in compliance with

the Strengthening the Reporting of Observational Studies in Epidemiology (STOBE) checklist.

Definitions

Bacteremia of hospital origin were defined according to the National Nosocomial Infections Surveillance Network (UHESA) (26).

Bacteremia was classified into two groups: Primary hospital-acquired bacteremia and bacteremia associated with previous healthcare facilities or applications. The former was defined as at least one positive blood culture taken from a patient after any time following 48 hours of hospitalization. The latter was defined as any positive blood culture obtained within the first 48 hours of hospitalization from a patient who had been receiving hemodialysis, wound care, chemotherapy, intravenous therapy, or nursing/home care, or who had applied to a hospital clinic within the past 30 days, or who had a history of hospitalization in the previous 90 days for ⩾2 days, or those living in a long-term care facility.

Primary bacteremia was defined as the detection of a positive blood culture for *Serratia* spp. in the absence of any other positive culture (urine, bronchoalveolar lavage, sputum, soft tissue). If *Serratia* spp. grew in any culture along with blood cultures, the primary site of infection was assumed to be the source where the positive culture had been obtained; thus, secondary bacteremia. The isolation of more than one organism from the same blood cultures was defined as polymicrobial bacteremia.

A disease outbreak was defined based on the World Health Organization criteria, as the occurrence and abrupt onset of affected cases of disease confirmed by positive cultures, exceeding what would normally be expected in a healthcare facility (27).

Previous antibiotic use was defined as use of an antibiotic for at least 48 h within the past month prior to the bacteremia episode. Appropriate therapy was defined as antibiotic therapy given based on the results of final blood cultures. Hypoalbuminemia was defined as a serum albumin level of less than 3.0 g/dL at the time of bacteremia.

The primary outcome was all-cause 30-day mortality after the first detection of *Serratia* spp. bacteremia.

Statistical Analysis

Data were processed with using Statistical Package for the Social Sciences (SPSS) 25 (IBM, Nyc, USA). Demographic and clinical characteristics and laboratory data of patients with primary hospital acquired bacteremia and those determined to have bacteremia possibly acquired from other healthcare facilities were compared. Categorical variables were presented as numbers (percentage), continuous variables were presented as means (standard deviation). The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of parameters. Variables without normal distribution were presented as medians with interquartile range (IQR). The non-parametric Mann-Whitney U test was used for comparison of numerical data, and the chi-squared test or Fisher's Exact test was used for comparison of categorical data. A p-value of less than 0.05 was considered significant.

Results

During the study period, *Serratia* spp. was sporadically identified in blood cultures of 47 patients. One patient who met the criteria for community-acquired bacteremia was excluded. Socio-demographic and clinical characteristics of 46 patients with primary hospital-acquired or with bacteremia acquired from previous healthcare facilities are summarized in Table 1. The majority of the patients were males (52.7%). The mean age of the patients was 60.7±17.6 years. The median hospital stay was 19.5 (IQR 8.8-55.8) days. Thirty-five patients (76.1%) were infected by *Serratia marcessens* (Table 1). All patients had predisposing risk factors for bacteremia, the most common being malignancies (n=19), followed by cardiac diseases (n=16), and diabetes mellitus (n=13) (Table 1).

Primary Hospital-acquired Bacteremia

Based on the inclusion criteria, 31 patients (67.4%) acquired *Serratia* spp. bacteremia while hospitalized at 13 diverse clinical and ICU settings, with anesthesia ICU being the most common (n=9), followed by cardio-vascular surgery (ICU) (n=5). Time from admission to laboratory detection of *Serratia* spp. ranged from 3 to 195 days (median 19; IQR 6-53). Detection of *Serratia* spp. fell into diverse time periods in all the 31 patients, with the shortest period being one month apart, ruling out the possibility of an outbreak. In this group the most common predisposing risk factors for bacteremia were being malignancies (n=13), cardiac diseases (n=12), and diabetes mellitus (n=9) (Table 1).

Bacteremia Acquired from Previous Healthcare Facilities

Within the first 48 hours of admission, blood cultures of 15 patients (32.6%) grew *Serratia* spp., all of whom had previous histories of healthcare: four patients had been receiving hemodialysis, three had been receiving chemotherapy, four had undergone major (n=2) or minor (n=2) surgical interventions, two had undergone urological interventions, one had been receiving homecare, and one had a history of hospitalization at another center. Of note, two patients also had a history of anesthesia with propofol for minor surgical interventions. In addition, five patients

had a previous history of antibiotic treatment in the past month.

Antibiotic Treatment

A history of antibiotic treatment in the past month was common (67.4%); 26 patients who acquired bacteremia in hospital settings had also taken antibiotics. All but one patient received empirical antibiotic therapy prior to or upon detection of *Serratia* spp. The rate of prior antibiotic use was significantly higher in patients with primary hospital-acquired bacteremia (p<0.01), so was the rate of appropriate empirical antibiotic use (p=0.01). Based on culture results and susceptibility testing, antibiotic therapy was revised so that 34 patients received appropriate antibiotic therapy.

Source of Bacteremia

The majority of cases (60.9%) were considered primary bacteremia, the remaining cases had respiratory tract infections (23.9%), urinary tract infections (6.5%) and surgical site infections (8.7%) responsible for *Serratia*

Table 1. Demographic and clinical characteristics of patients with *Serratia* spp. bacteremia

	Total (n=46)	Primary hospital-acquired bacteremia (n=31)	Bacteremia associated with previous healthcare facilities or applications (n=15)	p-value
Age (years), mean ± SD	60.7±17.6	60.3±16.1	61.6±21.1	0.57
Male, n (%)	24 (52.2)	17 (54.8)	7 (46.7)	0.60
Comorbidities n (%)	43 (93.5)	30 (96.8.0)	13 (86.7)	0.24
Malignancies	19 (41.3)	13 (41.9)	6 (40.0)	0.90
Cardiac diseases	16 (34.8)	12 (38.7)	4 (26.7)	0.42
Diabetes mellitus	13 (28.3)	9 (29.0)	4 (26.7)	0.87
Neurologic disorder	9 (19.6)	6 (19.4)	3 (20.0)	0.62
Chronic kidney disease	8 (17.4)	3 (9.7)	5 (33.3)	0.61
Chronic obstructive pulmonary disease	4 (8.7)	2 (6.5)	2 (13.3)	0.40
Source of bacteremia, n (%)				
Primary bacteremia	28 (60.9)	16 (51.6)	12 (80)	0.06
Secondary to respiratory tract infections	11 (23.9)	11 (35.5)	0 (0)	0.006
Secondary to urinary tract infections	3 (6.5)	1 (3.2)	2 (13.3)	0.24
Secondary to surgical-site infections	4 (8.7)	3 (9.7)	1 (6.7)	0.61
Polymicrobial bacteremia, n (%)	21 (45.7)	16 (51.6)	5 (33.3)	0.24
Sepsis	27 (58.7)	16 (51.6)	11 (73.3)	0.16
Monomicrobial bacteremia, n (%)	14 (51.9)	7 (43.8)	7 (63.6)	0.31
Polymicrobial bacteremia, n (%)	13 (48.1)	9 (56.2)	4 (36.4)	0.34
Hospital stay, median (IQR)	19.5 (8.8-55.8)	42 (18-82)	6 (2-12)	0.00
Time to positive cultures (days), median (IQR)	NA	19.0 (6.0-53.0)	NA	NA
Antibiotic treatment				
Antibiotic treatment in the past month, n (%)	31 (67.4)	26 (83.9)	5 (33.3)	0.001
Appropriate empirical antibiotic therapy, n (%)	27 (58.7)	22 (71.0)	5 (33.3)	0.01
Appropriate definitive antibiotic therapy, n (%)	34 (73.9)	23 (74.2)	11 (73.3)	0.61
Laboratory findings				
Hypoalbuminemia, n (%)	30 (65.2)	21 (67.7)	9 (60.0)	0.61
Procalcitonin, median (IQR)	9.1 (2.0-31.7)	8.8 (2.8-14.8)	24.4 (1.9-65.0)	0.26
Leukocyte count (×1000/uL), median (IQR)	14.29 (7.14-21.60)	13.10 (5.76-20.07)	18.01 (9.24-26.25)	0.24
Serum CRP (mg/L), median (IQR)	107.0 (24.5-261.0)	126 (27-261)	87 (10-261)	0.31
30-day mortality after detection of positive cultures	14 (30.4)	9 (29.0)	5 (33.3)	0.51

NA: Not applicable, CRP: C-reactive protein, IQR: Interquartile range, SD: Standard deviation

spp. bacteremia. Nearly half of the patients (45.7) had polymicrobial bacteremia, the great majority (76.2%) of whom acquired the infection in hospital settings. The most common coexisting bacterium was *Enterococcus* spp. (n=6), followed by *Pseudomonas* spp. (n=5).

Bacterial Resistance

On susceptibility testing, the highest rates of resistance were found to piperacillin/tazobactam (19.6%) and to carbapenems (19.6%) (Table 2). Resistance to piperacillin/tazobactam was significantly more common among patients with bacteremia previously acquired from healthcare facilities (p=0.02). Resistance to carbapenem among these cases was also higher than expected (20%).

Hospital Outcomes

During hospitalization, sepsis developed in 27 patients (58.7%). Within 30 days after laboratory detection of *Serratia* spp., mortality occurred in 14 patients (30.4%), with three patients dying within the first 24 hours of hospitalization.

Discussion

In our five-year review of *Serratia* spp., we identified 46 infected patients with primary hospital-acquired bacteremia or bacteremia acquired from previous healthcare facilities, all detected at diverse time points, highly excluding the possibility of an outbreak. Importantly, nearly a third of the cases (32.6%) were found to be associated with previous healthcare. Consistent with the literature reports, *Serratia* spp. bacteremia mostly developed in patients with comorbidities, in particular with malignancies, and in those having a previous history of antibiotic use (28,29,30).

Reports on *Serratia* spp. has been mainly concerned with hospital outbreaks, with reports on individual occurrences being rare (7,8,9,10,11,12,13,14,15,16,17,18). The outbreaks were mainly associated with therapeutic administration of contaminated magnesium sulphate (16), contaminated prefilled saline and/or heparin syringes (31), administration of propofol for anesthesia (11,12), use of contaminated pressure monitoring equipment (17), and use of contaminated epoetin alfa during hemodialysis (18).

Sunenshine et al. (16) documented a U.S. multistate outbreak of healthcare-acquired bloodstream infections in 18 patients from 5 states caused by *S. marcescens* transmitted via a contaminated commercial magnesium sulfate compound used for therapeutic purposes. During investigations for outbreaks of bloodstream infections, the authors emphasized the need to review the quality standards and use of commercial parenteral medications, such as magnesium sulfate, that are commonly used in hospital settings. Another U.S. multistate report of *S. marcescens* outbreak was concerned with bloodstream infections detected in 162 patients in whom contaminated prefilled saline and/or heparin syringes were used (31). In addition, as another source, outbreaks of *S. marcescens* emerged from inappropriate preparation, handling, storage, and use of propofol (11,12,13). Following detection of postoperative systemic inflammatory response syndrome in seven patients, *Klebsiella pneumoniae* and *S. marcescens* grew in cultures obtained from opened vials of propofol (12). The authors addressed problems concerning aseptic preparation, handling and storage of propofol that resulted in extrinsic contamination, particularly the use of a single-use vial for multiple patients. Another sepsis outbreak caused by *S. marcescens* from contaminated propofol was reported in three patients following chest surgery (11). These literature reports on *Serratia* spp. outbreaks clearly demonstrate that, whenever there has been a lapse or neglect in the sanitary standards and therapeutic applications, development of bacteremia is likely to be encountered in every setting of clinical practice. Harnett et al. (17) found contamination with *S. liquefaciens* in syringes and connector tubing of intravascular line pressure monitoring equipment, leading to positive blood cultures in 11 patients receiving adult critical care. The authors implicated lapses in hand hygiene during intravascular pressure monitoring. Finally, another outbreak of *S. liquefaciens* emerged from multiple use of preservative-free, single-use vials of epoetin alfa, where

Table 2. Antimicrobial resistance profile of all *Serratia* spp. isolates

Antimicrobial agents	All *Serratia* spp. isolates (n=46)	Primary hospital-acquired bacteremia (n=31)	Bacteremia associated with previous healthcare facilities or applications (n=15)	p-value
	Resistance rates, n (%)			
Quinolones	8 (17.4)	4 (12.9)	4 (26.7)	0.23
Third-generation cephalosporins	8 (17.4)	3 (9.7)	5 (33.3)	0.06
Carbapenems	9 (19.6)	6 (19.4)	3 (20.0)	0.62
Piperacillin/tazobactam	9 (19.6)	3 (9.7)	6 (40.0)	**0.02**
Trimethoprim/sulfamethoxazole	7 (15.2)	3 (9.7)	4 (26.7)	0.14

residual epoetin alfa was not discarded, but pooled and reused again in hemodialysis patients (18). The authors drew attention to the appropriate use of medication vials so that they contain a sufficient amount of medication for clinical need.

Despite a large number of hospital outbreaks reported associated with contaminated use of hospital medications and equipment, there has been a growing interest in attributing a greater role to community- or other healthcare-associated sources as the origin of *Serratia* spp. bacteremia. Two population-based studies reported considerably high rates of community-acquired or previously healthcare-associated *Serratia* spp. bacteremia (24,25). A laboratory surveillance study for *Serratia* spp. isolates in a large Canadian cohort over a six-year period found that 65% of incident *Serratia* spp. isolates were of community onset (25). Another population-based study from Australia over 10 years found that 29% of *Serratia* spp. bacteremia episodes were purely community-associated and a further 18% of episodes originated from community, but were in particular healthcare-associated (24). These findings about the community and/or previous healthcare origin of *Serratia* spp. bacteremia make our findings even more important and relevant, because, after a meticulous inquiry into the sources of cases, we found that 32.6% of our cases contracted bacteremia from healthcare delivered previously. This differentiation is particularly important in designing antibiotic treatment for these cases, as demonstrated by the significantly lower rate of appropriate empirical antibiotic therapy, addressing the need for a more comprehensive history taking about previous treatments and interventions in this patient group.

Concerning the source of bacteremia, 60.9% of patients had primary bacteremia, while 18 patients (39.1%) had secondary bacteremia. In addition, nearly half of the patients (45.7%) had polymicrobial bacteremia. The rates of both secondary bacteremia and polymicrobial bacteremia were higher in patients who acquired bacteremia at the hospital settings (Table 1). The high rate of polymicrobial bacteremia may be due to the presence of secondary bacteremia and longer hospital stays that may predispose patients to infections caused by other bacteria. Cultures of patients with polymicrobial bacteremia showed no growth of organisms suggestive of a possible contamination.

In our series, more than half of the patients (58.7%) developed sepsis, and mortality occurred in 30.4%. The rates of previously acquired *Serratia* spp. bacteremia from healtcare facilities and overall mortality were considerably higher compared to those reported in a similar study (for bacteremia, 32.6% vs. 18.4%; for mortality 30.4% vs. 22.4%) (32).

To our knowledge, there has been no report on comparative frequencies of *Serratia* spp. resistance to antibiotics in previously healthcare-associated and primarily hospital-acquired bacteremia. Our findings showed similar rates in the two bacteremia groups except for resistance to piperacillin/tazobactam, which was significantly more common (40% vs. 9.7%, p=0.02) among patients with previously healthcare-acquired bacteremia. Interestingly, resistance to carbapenem was even higher (20.0% vs. 19.4%) in this patient group (Table 2). These differences may result from the relatively small size of the two patient groups, the presence of long-term use of healthcare applications, such as hemodialysis (n=4) and chemotherapy (n=3) that may render the patients susceptible to antibiotic resistance, and the increased likelihood of lack or insufficiency of surveillance on antibiotic use or resistance in these healthcare facilities.

Study Limitations

The main limitation of the study is its retrospective design. The sample size is also smaller than other reported serious. Another limitation may be that, had a more comprehensive history concerning long-term previous use of antibiotics been obtained, a more detailed analysis and a more satisfactory explanation would have been possible about the differences in the rates of antibiotic resistance between the two groups.

Conclusion

The rate of bacteremia acquired previously from healthcare facilities is alarmingly high among hospitalized patients, which requires a meticulous inquiry into previous histories of patients so that appropriate empirical antibiotic therapy considering high rates of resistance can be designed and initiated. Whether or not detected during an outbreak, further comparative studies are required about the actual prevalence of *Serratia* spp. bacteremia acquired from community or from healthcare facilities other than the primary hospital setting.

Ethics

Ethics Committee Approval: The study was approved by the institutional review board of Pamukkale University with the decision numbered E. 310937 on 04.01.2023.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., S.O.K., F.S., A.K., İ.K., Concept: S.D., S.O.K., A.K., İ.K., Design: S.D., S.O.K., F.S., A.K., İ.K., Data Collection or Processing: S.D., S.O.K., F.S., A.K., İ.K.,

Analysis or Interpretation: S.D., S.O.K., F.S., A.K., İ.K., Literature Search: S.D., S.O.K., Writing: S.D., S.O.K.

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References

1. Ferreira RL, Rezende GS, Damas MSF, Oliveira-Silva M, Pitondo-Silva A, Brito MCA, et al. Characterization of KPC-producing Serratia marcescens in an intensive care unit of a Brazilian tertiary hospital. Front Microbiol. 2020;11:956. [Crossref]
2. Cristina ML, Sartini M, Spagnolo AM. Serratia marcescens infections in neonatal intensive care units (NICUs). Int J Environ Res Public Health. 2019;16:610. [Crossref]
3. Mahlen SD. Serratia infections: from military experiments to current practice. Clin Microbiol Rev. 2011;24:755-791. [Crossref]
4. Bloom R, Thakarar K, Rokas KE. Morbidity and mortality of Serratia marcescens bacteremia during the substance use epidemic. Int J Antimicrob Agents. 2023;62:106934. [Crossref]
5. Tavares-Carreon F, De Anda-Mora K, Rojas-Barrera IC, Andrade A. Serratia marcescens antibiotic resistance mechanisms of an opportunistic pathogen: a literature review. PeerJ. 2023;11:e14399. [Crossref]
6. Khanna A, Khanna M, Aggarwal A. Serratia marcescens- a rare opportunistic nosocomial pathogen and measures to limit its spread in hospitalized patients. J Clin Diagn Res. 2013;7:243-246. [Crossref]
7. Nelson GE, Greene MH. Enterobacteriaceae. In. Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia: Elsevier; 2020:2669-85. [Crossref]
8. Ulu Kilic A, Alp E, Orhan T, Cevahir F, Ersoy S, Altun D, et al. Clustering of Serratia marcescens infections during six years: epidemiology and risk factors for mortality. Canadian J Infection Control. 2017;32:104-107. [Crossref]
9. Fernández AL, Adrio B, Martínez Cereijo JM, Martínez Monzonis MA, El-Diasty MM, Alvarez Escudero J. Clinical study of an outbreak of postoperative mediastinitis caused by Serratia marcescens in adult cardiac surgery. Interact Cardiovasc Thorac Surg. 2020;30:523-527. [Crossref]
10. Merkier AK, Rodríguez MC, Togneri A, Brengi S, Osuna C, Pichel M, et al. Outbreak of a cluster with epidemic behavior due to Serratia marcescens after colistin administration in a hospital setting. J Clin Microbiol. 2013;51:2295-2302. [Crossref]
11. Cilli F, Nazli-Zeka A, Arda B, Sipahi OR, Aksit-Barik S, Kepeli N, et al. Serratia marcescens sepsis outbreak caused by contaminated propofol. Am J Infect Control. 2019;47:582-584. [Crossref]
12. Muller AE, Huisman I, Roos PJ, Rietveld AP, Klein J, Harbers JB, et al. Outbreak of severe sepsis due to contaminated propofol: lessons to learn. J Hosp Infect. 2010;76:225-230. [Crossref]
13. Bennett SN, McNeil MM, Bland LA, Arduino MJ, Villarino ME, Perrotta DM, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med. 1995;333:147-154. [Crossref]
14. de Frutos M, López-Urrutia L, Domínguez-Gil M, Arias M, Muñoz-Bellido JL, Eiros JM, et al. Serratia marcescens outbreak due to contaminated 2% aqueous chlorhexidine. Enferm Infecc Microbiol Clin. 2017;35:624-629. [Crossref]
15. Merino JL, Bouarich H, Pita MJ, Martínez P, Bueno B, Caldés S, et al. Serratia marcescens bacteraemia outbreak in haemodialysis patients with tunnelled catheters due to colonisation of antiseptic solution. Experience at 4 hospitals. Nefrologia. 2016;36:667-673. [Crossref]
16. Sunenshine RH, Tan ET, Terashita DM, Jensen BJ, Kacica MA, Sickbert-Bennett EE, et al. A multistate outbreak of Serratia marcescens bloodstream infection associated with contaminated intravenous magnesium sulfate from a compounding pharmacy. Clin Infect Dis. 2007;45:527-533. [Crossref]
17. Harnett SJ, Allen KD, Macmillan RR. Critical care unit outbreak of Serratia liquefaciens from contaminated pressure monitoring equipment. J Hosp Infect. 2001;47:301-307. [Crossref]
18. Grohskopf LA, Roth VR, Feikin DR, Arduino MJ, Carson LA, Tokars JI, et al. Serratia liquefaciens bloodstream infections from contamination of epoetin alfa at a hemodialysis center. N Engl J Med. 2001;344:1491-1497. [Crossref]
19. Do RR, Shravan-Turaga NS, Patel R, Patel J, Brown D. An unusual culprit for endocarditis. Chest. 2018;154:53. [Crossref]
20. Wu YM, Hsu PC, Yang CC, Chang HJ, Ye JJ, Huang CT, et al. Serratia marcescens meningitis: epidemiology, prognostic factors and treatment outcomes. J Microbiol Immunol Infect. 2013;46:259-265. [Crossref]
21. Theccanat G, Hirschfield L, Isenberg H. Serratia marcescens meningitis. J Clin Microbiol. 1991;29:822-823. [Crossref]
22. Shiyin Z, Anil S, Nina R, Stephen P, Neil H. Community-acquired severe soft tissue infection due to Serratia marcescens in an immunocompetent host. Chest. 2014;146(Suppl 2):141. [Crossref]
23. Rallis E, Karanikola E, Papadakis P. Severe facial infection caused by Serratia marcescens in an immunocompetent soldier. J Am Acad Dermatol. 2008;58(Suppl 1):109-110. [Crossref]
24. Engel HJ, Collignon PJ, Whiting PT, Kennedy KJ. Serratia sp. bacteremia in Canberra, Australia: a population-based study over 10 years. Eur J Clin Microbiol Infect Dis. 2009;28:821-824. [Crossref]
25. Laupland KB, Parkins MD, Gregson DB, Church DL, Ross T, Pitout JD. Population-based laboratory surveillance for Serratia species isolates in a large Canadian health region. Eur J Clin Microbiol Infect Dis. 2008;27:89-95. [Crossref]
26. Ulusal Sağlık Hizmeti İlişkili Enfeksiyonlar Sürveyans Rehberi. Sağlık Bakanlığı. 2017. Ankara. [Crossref]
27. Workd Health Organization regional Office For The Eastern Mediterranean Disease outbreaks. [Crossref]
28. de Boer MG, Brunsveld-Reinders AH, Salomons EM, Dijkshoorn L, Bernards AT, van den Berg PC, et al. Multifactorial origin of high incidence of Serratia marcescens in a cardio-thoracic ICU: analysis of risk factors and epidemiological characteristics. J Infect. 2008;56:446-453. [Crossref]
29. van der Sar-van der Brugge S, Arend SM, Bernards AT, Berbee GA, Westendorp RG, Feuth JD, et al. Risk factors for acquisition of Serratia marcescens in a surgical intensive care unit. J Hosp Infect. 1999;41:291-299. [Crossref]
30. Voelz A, Müller A, Gillen J, Le C, Dresbach T, Engelhart S, et al. Outbreaks of Serratia marcescens in neonatal and pediatric intensive care units: clinical aspects, risk factors and management. Int J Hyg Environ Health. 2010;213:79-87. [Crossref]
31. Blossom D, Noble-Wang J, Su J, Pur S, Chemaly R, Shams A, et al. Multistate outbreak of Serratia marcescens bloodstream infections caused by contamination of prefilled heparin and isotonic sodium chloride solution syringes. Arch Intern Med. 2009;169:1705-1711. [Crossref]
32. Kim SB, Jeon YD, Kim JH, Kim JK, Ann HW, Choi H, et al. Risk factors for mortality in patients with Serratia marcescens bacteremia. Yonsei Med J. 2015;56:348-354. [Crossref]