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REVIEW

A common problem in primary care; elbow pain and developing an easy-to-approach algorithm

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ABSTRACT

Elbow pain is a common complaint in primary care. It can originate from any part of the joint such as tendons, bursae, bones. Elbow pain can occur at any time in life with varying accompanying symptoms. Situations that will require the primary care physician to be alerted; Swelling and dislocation after trauma, swollen joint or rapidly increasing mass. It means that 85% of the diseases seen in the society can be treated with a well-trained family physician specialist. This, in turn, eases the burden of the second and third levels, provides easier access to the patient in need of the upper level and provides a cost-effective healthcare service. In primary care, it is the first point of contact for patients with diseases that are common in the community. A detailed anamnesis, correct examination request, treatment and then follow-up examination, gradual referral to the second step, ascribes an indispensable role to the first step in the diagnosis, treatment and solution of many diseases.

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The elbow is a complex joint designed to withstand a wide range of dynamic strain forces. Elbow pain is a common complaint in primary care. This complaint; It can originate from any part of the joint such as tendons, bursae, bones. Tendinopathies such as lateral and medial epicondylitis can be caused by some sports and routine activities in my daily life [1].

Elbow pain can occur at any time in life with varying accompanying symptoms. Situations that will require the primary care physician to be alerted; Swelling and dislocation after trauma, swollen joint or rapidly increasing mass.

The location and severity of elbow pain is usually localized to one of four anatomical sites: anterior, medial, lateral, or posterior. The pain described in each of these regions has a key role in leading us to different diagnoses [2]. (Table 1)

Stiffness with elbow pain is associated with arthritis or trauma. Neurological complaints such as numbness and tingling sensation extending to the fingertips are usually accompanied by tendinopathies, osteoarthritis (50% of patients) and inflammatory arthritis [3]. Pain radiating from the neck or shoulder may occur as elbow pain, cervical disc disorders should not be forgotten in the differential diagnosis [1].

The pain that can be localized by the patient in the arm with pain radiating to the forearm, tenderness in the lateral epicondyle, a traumatic elbow pain, may be the characteristic initial sign of lateral epicondylitis [3]

Table 1. Clinical findings according to types of elbow pain

Sensitivity Zone	Diagnosis	Clinical Appearance	Diagnostic Approach	Treatment
Anterior	Biceps tendinopathy	anterior elbow pain; history of forearm supination and pronation recurrent pain	Pain in the antecubital fossa of the elbow forced into supination	Rest Ice short term NSAI Physiotherapy
Lateral	Lateral epicondylitis	It is more common in medial epicondylitis; Insidious onset, pain on repetitive movements, tension on palpation of the extensor tendon	Decreased pain and strength, decreased pain and strength in supination and extension, pain in the lateral elbow and resistance to extension in the middle finger	Rest Ice short term NSAI Stretching and strengthening exercise corticosteroid injection PRP topical nitroglycerin Surgery in missed cases
Lateral	Posterior interosseous nerve syndrome	Inability to extend middle finger against resistance	Middle finger test positive result	Reduce exposure splint Ergonomics Strengthening and stretching exercises Missed case surgery
Lateral	radial tunnel syndrome	Pain in the lateral forearm, no motor symptoms	just pain	Reduce exposure splint Ergonomics Strengthening and stretching exercises Missed case surgery
Posterior	Aseptic olecranon bursitis	History of minor trauma to the elbow Feeling of a non-tense mass on the olecronon	Absence of other signs of infection such as redness, warmth, limitation of movement, Bursa fluid analysis,	Ice Printed dressing Reducing exposure Fluid aspiration from the bursa in those who do not respond to a tight bandage for 2 weeks Surgical bursectomy in cases lasting longer than 3 months Intra-bursa corticosteroid injection
Posterior	Septic olecranon bursitis	Pain, increased temperature, discharge, erythema over the olecranon and increased temperature edema, 50% fever	Bursa sıv Bursa fluid analysis ı analizi	aspiration mechanical rest Systemic oral/iv antibiotic (according to culture result)
Posterior	Posterior trauma	Pain in the posterior elbow, especially in full extension	Back elbow pain when elbow is forced into full extension X-RAY: Finding of osteophyte formation	Preventing uncomfortable movements Surgery for osteophytes if conservative treatment fails
Posterior	Triceps tendinopathy	Pain behind the elbow when using the extensor	Pain behind the elbow in forced extension, tenderness in the triceps insertion	Rest Ice short term NSAI Physiotherapy Rarely, surgery may be required.
Medial	cubital tunnel syndrome	Insidious onset of pain and paresthesia in the medial part of the forearm to the ring and little finger	Tinel test positivity Feeling of flexion and extension ulnar nerve subluxation in the medial epicondyle	reduce exposure Night splint to keep the arm in extension nerve glide exercise Surgery in cases unresponsive to treatment
Medial	medial epicondylitis	Insidious onset of pain Tension on palpation of the flexor pronator muscle	Resistance in shoulder flexion and pronation	Rest Ice Short-term topical or oral NSAI Stretching and strengthening exercises corticosteroid injection PRP topical nitro Surgery in missed cases
Medial	Ulnar collateral ligament injury	Pop sensation on the medial elbow side	Milking maneuver positive, valgus stress test positive	Rest Ice Short-term topical or oral NSAI Grade 1-2 physiotherapy Surgery in professional athletes in the early period

Pain that increases with activity catching an object localized to the medial side of the elbow is due to medial epicondylitis, also known as 'golfer's elbow'. Recurrent stress and trauma history should be questioned [3].

Findings such as limitation of the final range of elbow opening and closing movements and prolonged progressive pain and locking indicate osteoarthritis [1]. Bilateral elbow pain, stiffness, joint swelling, complete loss of elbow opening and closing or involvement of other joints, and systemic symptoms indicate inflammatory arthritis, because in 20-50% of patients with rheumatoid arthritis (RA), elbow involvement accompanies RA [4].

Before the examination of the patient with elbow pain, the Spurling test is performed, which shows the pain when pressing the elbow head while extending the pressure to the side and turning the head to exclude extra-elbow pathologies, especially cervical nerve compression. After excluding cervical pathologies, examination of the elbow begins. It is always evaluated together with the other party during the examination. Identify the most painful part of the joint when touched, check if there is a palpable mass. If there is redness, tenderness, swelling on the joint, question the trauma situation and differentiate between inflammatory processes and traumatic processes. Check the duration of the pain with which movements it increases or decreases. Consider biceps tendinitis in the differential diagnosis in case of tenderness anterior to the antecubital fossa. Do the Tinel test, if positive, decrease medial epicondylitis. Point tenderness on the lateral elbow is diagnostic for lateral epicondylitis [4]. Make elbow opening and closing movements, if the limitation in this movement is unilateral, it is in favor of osteoarthritis. Finally, do your other system examinations. If any systemic symptom accompanies elbow pain, consider inflammatory rheumatological processes in the differential diagnosis. (Figure 1)

Complete blood count, erythrocyte sedimentation rate, and rheumatoid factor tests should be requested if inflammatory arthritis is suspected. Direct plain radiographs are normal in tendinopathies and do not need to be requested [5]. Ultrasound scanning requires experience and its sensitivity and specificity may vary depending on the operator [4]. When ligament injury is considered, magnetic resonance imaging is useful and the patient should be referred to the second step [3].

TREATMENT

The aim of treatment should be to eliminate the pain or at least to minimize it so that it does not affect daily life. Treatment options such as joint rest and oral and injective analgesics relieve pain. The treatment in tendinopathies should be to relieve the load of the joint and to increase the strength of the injured tendon [1]. The patient should limit all activities that aggravate the pain in the joint. Tape application on the muscle body reduces the load on the joint [5]. Physiotherapy also increases muscle strength and reduces the stress of the joint against the tolerated load [1]

Application of physiotherapy for a period of 1 year has been shown to be 91% effective in the regression of symptoms [6]. Although corticosteroid injections regress short-term complaints, it should be avoided as they may lead to worse results in the long term [7]. The use of botulinum toxin and platelet-rich plasma to treat tendinopathies has increased in the last 5 years, but there is no clinical evidence of superiority over placebo [5]. Referral to care to a secondary care provider is indicated after symptoms persist despite 6-12 months of conservative treatment. However, outcomes after surgery are variable, as 25% of patients who have surgery still have pain in the first postoperative year. Arthritis can be treated non-surgically with regulation of daily activities, NSAIDs, steroids, splinting, ice, or the use of heat.

When to consider referral to the upper echelon

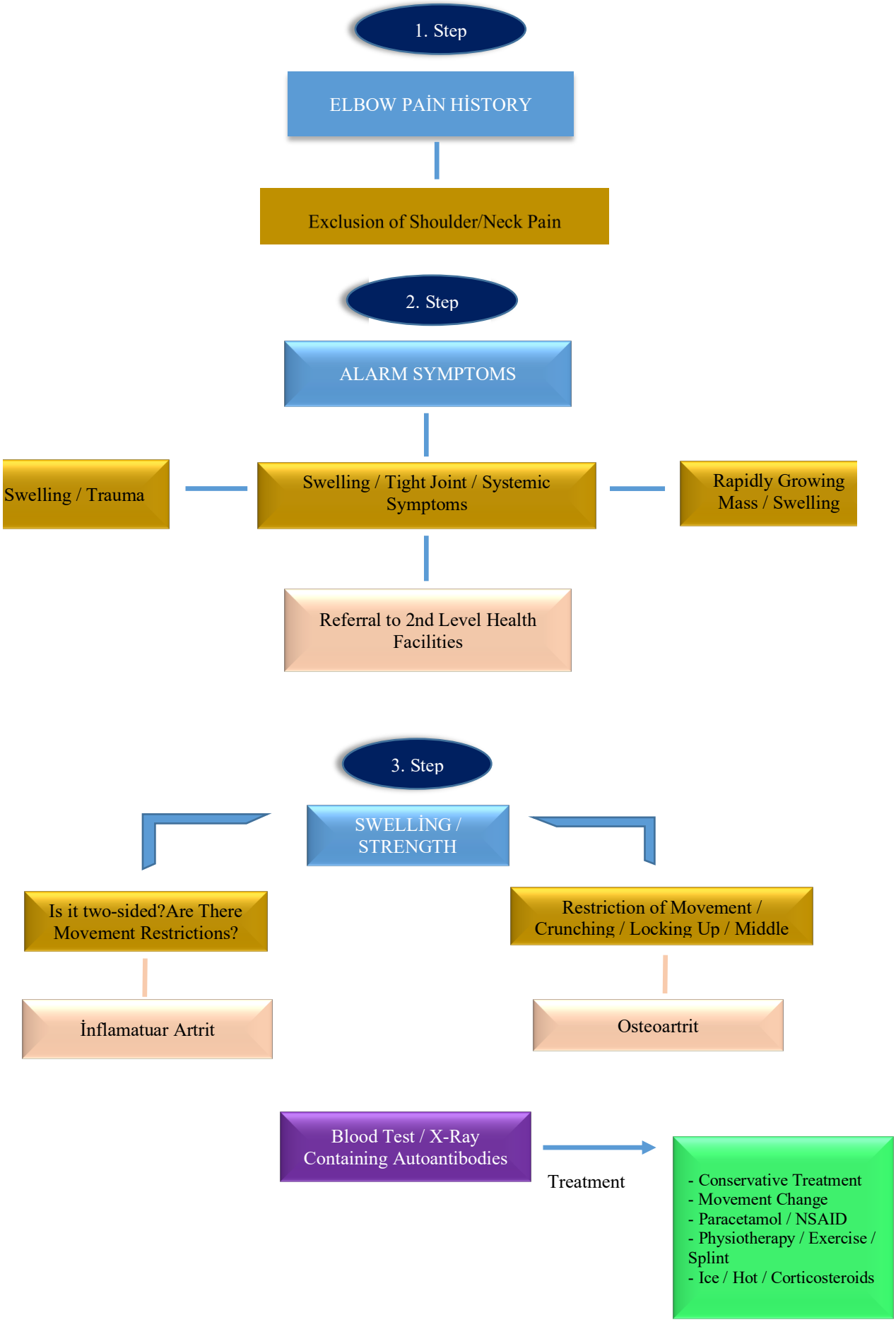
Indications for referral to secondary care [8]

- Pain not responding to all non-surgical interventions
- impair the quality of daily life
- painful locking of the elbow and inability to move

The first-line treatment of painful elbow conditions can be resolved with long-term conservative treatment, rehabilitation exercises and the patient's continuity [9]. Occupational and daily exposure-related distress causing elbow pain is more resistant to nonsurgical treatment. In this case, you may consider giving the patient a short rest to rest the joint and perform strengthening exercises. It should not be forgotten that follow-up is an indispensable part of the treatment and should be done in a period specific to the patient.

CONCLUSION

It means that 85% of the diseases seen in the society


1. Step
ELBOW PAİN HİSTORY
Exclusion of Shoulder/Neck Pain
2. Step
ALARM SYMPTOMS
Swelling / Trauma
Swelling / Tight Joint / Systemic Symptoms
Rapidly Growing Mass / Swelling
Referral to 2nd Level Health Facilities
3. Step
SWELLİNG / STRENGTH
Is it two-sided?Are There Movement Restrictions?
Restriction of Movement / Crunching / Locking Up / Middle
İnflamatuar Artrit
Osteoartrit
Blood Test / X-Ray Containing Autoantibodies
Treatment
- Conservative Treatment
- Movement Change
- Paracetamol / NSAID
- Physiotherapy / Exercise / Splint
- Ice / Hot / Corticosteroids

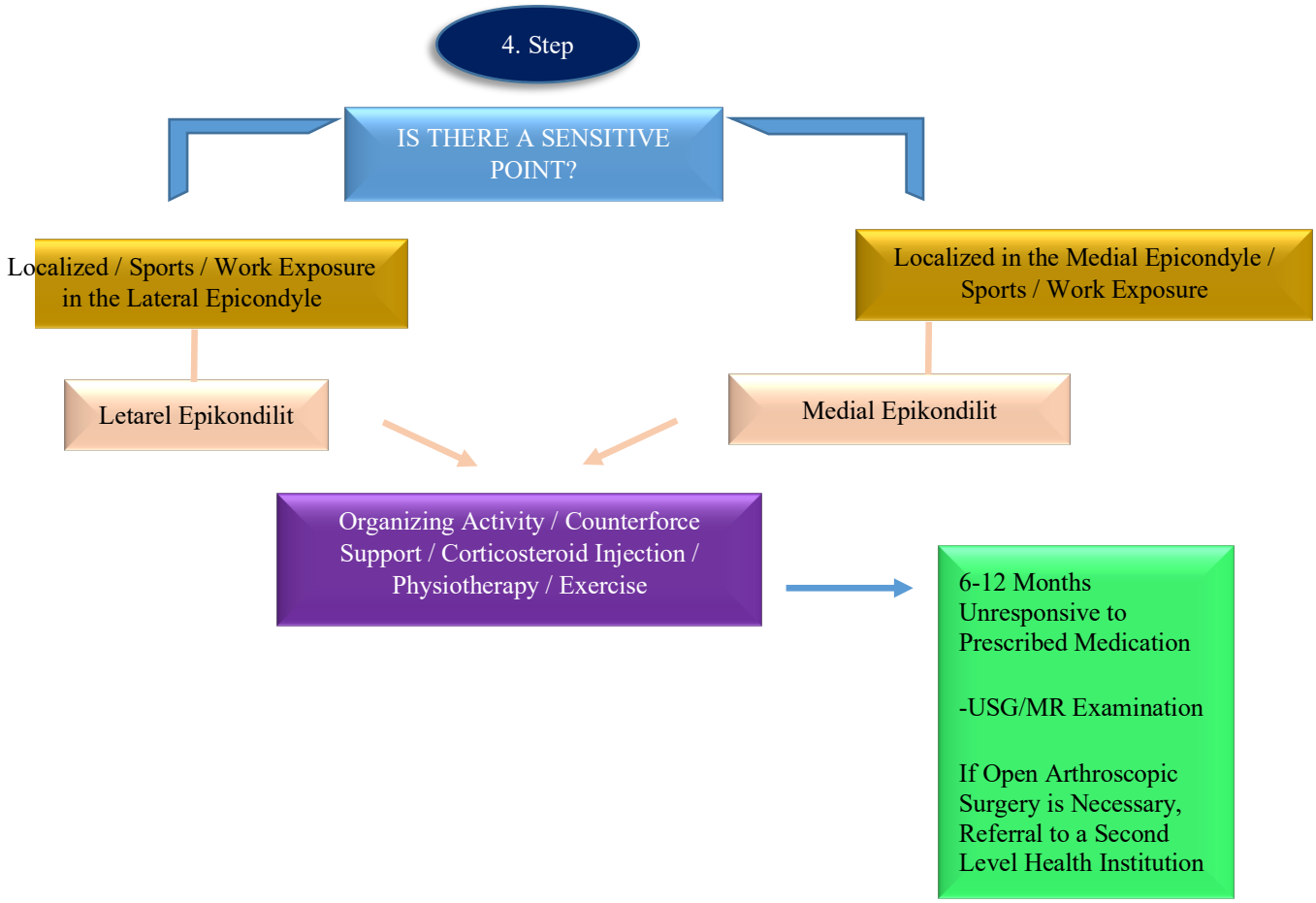


Figure 1. Algorithm for approach to elbow pain

can be treated with a well-trained family physician specialist. This, in turn, eases the burden of the second and third levels, provides easier access to the patient in need of the upper level and provides a cost-effective healthcare service. In primary care, it is the first point of contact for patients with diseases that are common in the community. A detailed anamnesis, correct examination request, treatment and then follow-up examination, gradual referral to the second step, ascribes an indispensable role to the first step in the diagnosis, treatment and solution of many diseases.

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Conflict of interest

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Ethical approval

Ethics committee approval was not required as this study was written as a reviwer.

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ORIGINAL ARTICLE

Clinic Analysis of Adult Patients with Acute Lymphoblastic Leukemia

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ABSTRACT

Objectives: In this study, it was aimed to evaluate the demographic and clinical characteristics, prognostic factors, response to different treatment options, side effects caused by changing treatment choices, and overall survival rates of adult Acute Lymphoblastic Leukemia (ALL) patients.

Methods: Our study included 44 patients aged 18 and over, who were followed up with the diagnosis of ALL in our hematology clinic, and treated with treatment protocols containing hyperCVAD (cyclophosphamide, vincristine, Adriamycin, dexamethasone) chemotherapy regimen. Patients were classified according to their clinical findings, organ involvement, and demographic data at the time of diagnosis. The treatment response rates and treatment complications were compared.

Results: The median age of 44 patients included in the study was 34, 72.2% were male, and 27.7% were female. It was determined that 61% of the patients had B cell immunophenotype, and 6 (13.6%) had Philadelphia (+). The rate of the high-risk patient group was 81.8%. The complete remission rate was 72.7%, and the overall survival rate was 43.1%. It was observed that treatment-related sepsis and death rates increased, and complete remission rates and total survival time decreased in patients who added L-asparaginase to the HyperCVAD treatment regimen.

Conclusion: It was observed that the results obtained in our study were similar to other studies. It has been concluded that the current treatment options are not sufficient for adult ALL patients with a total survival rate of 27%, and new treatment protocols are required.

Acute lymphoblastic leukemia (ALL) is a malignant disease characterized by clonal proliferation of lymphocyte precursors (consisting of 80-85% B cell precursors, 15-20% T cell precursors) [1, 2]. It constitutes approximately 85% of childhood acute leukemias and approximately 15% of adult leukemias [3, 4]. In addition to being more common in men, it is known that diseases such as Down syndrome, Bloom's syndrome, Fanconi anemia, and ataxia-telangiectasia are hereditary disorders that predispose to ALL, and the risk of ALL increases after exposure to ionizing radiation [5].

Signs and symptoms in ALL occur

with bone marrow infiltration and suppression of normal hematopoiesis. The most common signs and symptoms are pallors, fatigue, fever, bone, and joint pain, organomegaly, and lymphadenopathy [3]. The FAB (French-American-British) classification is basically based on morphological features and has limited significance in terms of prognosis and guiding treatment. The WHO (World Health Organization) classification system has started to be used more widely. The treatment of ALL consists of chemotherapy regimens with a combination of cytotoxic drugs [5].

Clinical parameters, immunophenotyping, cytogenetic analysis, treatment response, and minimal residual disease are the primary indicators used in risk stratification in ALL patients today [6].

It was aimed to evaluate the demographic and clinical characteristics, prognostic factors, response to different treatment options, side effects caused by changing treatment choices, and overall survival rates of adult ALL patients in this study.

METHODS

Our study, which was planned in accordance with the Helsinki Declaration decisions, the patient rights regulation, and ethical rules, started after the approval of Medical Research Ethics Committee with the decision numbered 2015-19/19.

A total of 44 patients diagnosed with ALL that received the hyperCVAD chemotherapy protocol, including regimens as a remission induction therapy in Hematology Department outpatient clinic, were included in this study. The data of the patients were obtained from the electronic medical records and follow-up files. Patients older than 18 years of age, diagnosed with ALL by histopathology and flow cytometry, and receiving hyperCVAD included chemotherapy protocol were included in the study.

All patients' symptoms at the time of diagnosis, medical histories, and physical examination information were retrospectively scanned from

Table 1. Characteristics of the patients at the time of diagnosis

Age, median (min-max)	34 (20-62)
Gender, n(%)	
Male	32 (72.2)
Female	12 (27.7)
ECOG performance status, median(min-max)	1.27 (0-4)
Patients with B symptoms, (%)	93
Involvements, (%)	
Hepatomegaly	15.9
Splenomegaly	47.7
Lymphadenopathy	43
Mediastinal mass	4
Central nervous system leukemia	9
Testicular involvement	0
Pericardium	4
Pleura	2
Skin	2
Immunophenotype, n (%)	
Mature T Cell ALL	12, (27.2)
Precursor T-Cell ALL	1, (2.2)
Mature B-Cell ALL	19, (43.1)
Precursor B Cell ALL Calla (+)	5, (11.3)
Precursor B Cell ALL Calla (+) (Myeloid Expression+)	1, (2.2)
CML Transformed Precursor B-Cell ALL	2, (4.5)
Biphenotypic ALL	2, (4.5)
Lymphoma in T Cell Leukemia Form	1, (2.2)
Lymphoma in Precursor T-Cell Leukemic Form	1, (2.2)

ECOG: Eastern Cooperative Oncology Group

their files. Complete blood count, peripheral smear, serum electrolyte measurements, kidney function tests, hepatic enzymes, coagulation tests, and Lactate dehydrogenase value of the patients were noted. The results of chest X-ray, cranial imaging, and cerebrospinal fluid examination performed to evaluate systemic involvement were recorded. Cytogenetic, immunophenotypic, and morphological evaluations studied from bone marrow aspiration and biopsy were filed.

Descriptive statistics for categorical variables were given as frequency and percentage, and continuous variables were given as median (minimum-maximum). Fischer's exact chi-square test was used to compare categorical variables between groups, and the Mann-Whitney U test was used for intergroup comparison of continuous variables. Median survival values, standard errors, confidence intervals, and survival graphs were obtained by using the Kaplan-Meier method. Analyzes were made in IBM SPSS v.21 software. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 44 patients included in the study, 42 were diagnosed with ALL, one with T-cell lymphoma in the leukemic form, and one with lymphoma in the Precursor T-cell leukemic form. The median age of the patients was 34 (20-62), 32 patients (72.2%) were male, and 12 patients (27.7%) were female. (Table-1)

While 39 (88.6%) of the patients were in the high-risk group, 5 (11.3%) were in the standard-risk group. Of the patients with a mean ECOG performance of 1.27 (0-4) at the time of diagnosis, 15.9% had hepatomegaly, 47.7% splenomegaly, 43% lymphadenopathy, 4% mediastinal mass, and 9% central nervous system involvement was observed. No patient with testicular involvement was detected at the time of diagnosis. When evaluated in terms of other organ involvement, pericardial involvement, pleural involvement, skin involvement, and myometrial involvement were observed in 2,1,1 and 1 patients, respectively (Table 1).

While the number of patients with L1, L2, and L3 morphology was 2 (4.5%), 23 (52.2%), and 3 (6.8%), respectively, morphological typing information of 16 patients could not be reached. In the immunophenotypic evaluation, It was determined that 27.2% of the patients had mature T-cell ALL, 2.2% had precursor T-cell ALL, 43.1% had mature B-cell ALL, 11.3% had precursor B-cell ALL Calla(+), 2.2% precursor B-cell ALL Calla(+) with myeloid expression, 4.5% CML-transformed precursor B-cell ALL, 4.5% bi-phenotypic ALL, 2.2% T-cell ALL lymphoma in the leukemic form and 2.2% of them were lymphoma in the precursor T-cell leukemic form (Table 1).

At the time of diagnosis, the median leukocyte count was 73,967 (1,500-662,000), the neutrophil count was 6,268 (0-53,300), the platelet count was 106,481 (6,000-677,000), hemoglobin level was 9.35(4-15.2), lactate dehydrogenase (LDH) level was 1.625 (79-7,500). While the blast rate was 86.69% in the bone marrow, it was 60.3% in the peripheral blood (Table 2). No cytogenetic anomaly was detected in 38 (87%) of the patients, while Ph(+) was detected in 6 (13%) patients (Table 2).

The degree of toxicity developed with remission induction therapy, including a hyperCVAD chemotherapy regimen, is shown in the table (Table 3). After remission induction therapy, 32 (72.7%) of the patients were in complete remission, but relapse was observed in half of them (16 patients) during the follow-up period. Twenty-five (56.8%) of the patients included in the study died during the follow-up period. Of the 9 (20.4%) patients who died during remission induction therapy, six died due to sepsis and related complications, and three died due to bleeding.

It was found that the rate of achieving complete remission was not related to the gender distribution of the patients (81.3% male vs. 18.8% female, $p = 0.213$). It was observed that the presence of hepatomegaly,

Table 2. Laboratory characteristics of the patients at the time of diagnosis

	Median (min-max)
White Blood Cells (K/µL)	73,967 (1,500-662,000)
Neutrophil (K/µL)	6,268 (0-53,300)
Hemoglobin (g/dl)	9.35 (4-15.2)
Platelet (K/µL)	106,481 (6,000-677,000)
Lactate dehydrogenase (IU/L)	1,625 (79-7,500)
Blast rate in bone marrow, (%)	86.69
Blast rate in peripheral blood, (%)	60.3

Table 3. Chemotherapy toxicities					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Gastrointestinal	59.0	29.5	4.5	4.5	2.2
Hematological	2.2				97.7
Renal	90.9	6.8	2.2		
Neuromuscular		2.2			
Cardiovascular		2.2		2.2	
Dermatological		6.8		2.2	
Hepatic	72.7	4.5	15.9	2.2	4.5
All parameters are given as a percentage.					

splenomegaly, and mediastinal mass did not affect the rate of complete remission in the patients (p = 1.00). Although complete remission was achieved in 4 of 6 patients with Philadelphia (+), it was observed that this did not affect the complete remission rate (p = 0.616). It was observed that 32 (72.7%) of the 42 patients with risk scoring were in the high-risk category, 87.5% of the patients in complete remission were in the high-risk group, and 12.5% of them were in the standard-risk group. No significant relationship was observed between the risk scoring of the patients and the rates of achieving complete remission (Table 4).

A comparison of complete remission rates in terms of immunophenotype and morphological type could not be made due to the insufficient number of patients in the subgroups. The proportional evaluations of these variables and their subgroups are given in Table 5.

When the effects of risk scoring, treatment regimen difference, and presence of cytogenetic anomaly on the recurrence rates of patients in complete remission after remission induction therapy were examined, no statistically significant difference was observed between the presence of recurrence and cytogenetic anomaly (Table 6, p = 1.00).

ALL patients in our study received four different treatment regimens (hyperCVAD, HyperCVAD + L-asparaginase, hyperCVAD + dasatinib, and hyperCVAD + dasatinib + L-asparaginase) as remission induction therapy (7-10). Statistical analyzes were performed on effects, side effects, mortality, and survival among these treatment regimens. Patients who received remission induction therapy with hyperCVAD + dasatinib and hyperCVAD + dasatinib + L-asparaginase combination regimens were not included in the statistical comparisons due to insufficient data. Significant differences were observed in the treatment-related sepsis frequency,

Table 4. Comparisons made about achieving complete remission			
	Complete Remission (+) n = 10	**Complete Remission (–) n = 32**	***P***
Gender, n (%)			
Male	6 (60)	26 (81.3)	0.213
Female	4 (40)	6 (18.8)	
Hepatomegaly, n (%)			
Exist	1 (10)	6 (18.8)	1.000
None	9 (90)	26 (81.3)	
Splenomegaly, n (%)			
Exist	4 (40)	15 (46.9)	1.000
None	6 (60)	17 (53.1)	
Mediastinal Mass, n (%)			
Exist	0 (0)	2 (6.3)	1.000
None	10 (100)	30 (93.8)	
Cytogenetic anomaly, n (%)			
t(9.22) Positive	2 (20)	4 (12.5)	0.616
t(9.22) negative	8 (80)	28 (87.5)	
Risk score, n (%)			
Standard risk	2 (20)	4 (12.50)	0.616
High risk	8 (80)	28 (87.50)	

Table 5. Distribution of variables related to complete remission achieving		
	Complete Remission (+) n = 10	**Complete Remission (–) n = 32**
Immunophenotype, n (%)		
Mature T Cell ALL	4 (40)	7 (21.90)
Precursor T-Cell ALL	0 (0)	1 (100)
Mature B-Cell ALL	4 (40)	14 (43.80)
Precursor B Cell ALL Calla(+)	1 (10)	4 (12.50)
Precursor B Cell ALL Calla(+)(Myeloid Expression+)	0 (0)	1 (3.10)
CML Transformed Precursor B-Cell ALL	0 (0)	2 (100)
Biphenotypic ALL	1 (10)	1 (3.10)
Lymphoma in T Cell Leukemia Form	0 (0)	1 (3.10)
Lymphoma in Precursor T-Cell Leukemic Form	0 (0)	1 (3.10)
Morphological type, n (%)		
L1	1 (16.70)	1 (4.50)
L2	5 (83.30)	17 (77.30)
L3	0 (0)	3 (13.60)

death during treatment, and complete remission rates with the treatment regimen applied. Comparing HyperCVAD with HyperCVAD + L-Asparaginase treatment, sepsis rates (5 (15.2%) vs. 4 (57.1%), p = 0.034), the mortality rate (5 (15.2%) vs. 4 (57.1%), p = 0.034) It was observed that the rate of complete remission (26 (81.3%) vs. 2 (33.3%), p = 0.031) was lower (Table 7).

The applied treatment regimen and achieving complete remission were found to be effective in overall survival. The total survival time of all patients who received a treatment protocol, including the HyperCVAD chemotherapy regimen, was calculated as 530 ± 106.10 days. It was observed that the total survival time was longer in patients with complete remission (1021.23 ± 174.72 days vs. 70.11 ± 20.42 days, $p < 0.001$). While total survival was observed as 603 ± 75 days in patients receiving the HyperCVAD chemotherapy regimen, total survival time was found to be 17 ± 4.9 days in patients receiving HyperCVAD + L-asparaginase combined therapy (Table 8).

The disease-free survival time of all patients was determined as 499 ± 117.68 days. There was no effect of hepatomegaly, splenomegaly, and cytogenetic abnormality on disease-free survival (Table 9).

DISCUSSION

The prognosis of ALL patients varies according to patient and disease characteristics. Age, performance status, organ functions, immunophenotype, karyotype, accompanying cytogenetic anomaly, leukocyte count at diagnosis, time to complete remission, and presence of minimal residual disease are shown as risk factors affecting prognostic indicators in adult patients [1, 3, 11-13]. According to these characteristics, patients are divided into groups low-risk (standard-good-risk) and high-risk (poor-risk) patients [12]. While the disease-free survival rate was 50-60% in the standard-good-risk patient group, this rate was found to be 20% or less in the high-poor-risk patient group. High-risk patients are seen in 75% of adult ALL patients [11-13]. In the current study, the rate of high-risk patients was found to be 81.8%.

ALL constitutes approximately 20% of adult acute

Table 6. Comparisons of recurrence rate			
	No Recurrence n = 15	**Recurrence n = 16**	***p***
Cytogenetic anomaly, n (%)			1.000
t(9.22) Positive	2 (3.30)	2 (12.50)	
t(9.22) negative	13 (86.70)	14 (87.50)	

Table 7. Comparisons with the applied treatment regimen			
	HyperCVAD n = 33	**HyperCVAD + L-Asparaginaz n = 7**	***p***
Frequency of treatment-related FEN			
Exist	23 (%69.70)	6 (%85.70)	0.650
None	10 (%30.30)	1 (%14.30)	
Frequency of treatment-related sepsis			
Exist	5 (%15.20)	4 (%57.10)	**0.034**
None	28 (%84.80)	3 (%42.90)	
Side Effects			
Gastrointestinal	0 (0-3)	1 (0-3)	0.382
Hematological	4 (0-4)	4 (4-4)	0.917
Renal	0 (0-0)	0 (0-1)	0.081
Neuromuscular	0 (0-2)	0 (0-0)	0.917
Cardiovascular	0 (0-0)	0 (0-4)	0.577
Dermatological	0 (0-3)	0 (0-0)	0.626
Hepatic	0 (0-3)	0 (0-4)	0.382
Mortality during treatment			
Excitus	5 (%15.20)	4 (%57.10)	**0.034**
Alive	28 (%84.80)	3 (%42.90)	
Complete remission			
No Remission	6 (%18.80)	4 (%66.70)	**0.031**
Remission	26 (%81.30)	2 (%33.30)	
Recurrence rate			
Exist	14 (%56)	0(%0)	0.222
None	11 (%44)	2(%100)	
FEN: Febrile neutropenia			

leukemia. The most common B cell immunophenotype is seen in adult patients with ALL [5, 6]. In our study, it was observed that 61% of the patients had B cell immunophenotype.

While there is no difference in the incidence of ALL in childhood, the male gender comes to the fore in adulthood [4]. It was found to be more common in males, with a rate of 72.2% in the current study. Approximately 2/3 of childhood ALL cases are cured after treatment. This rate decreases to 1/3 in adulthood [4].

Cytogenetic anomaly is seen in 80% and 60-70% of childhood and adult ALL cases, respectively [6]. In our study, in which t(9:22) mutation was observed to be positive in 6 (13.6%) of the 44 patients included in the study, the most common cytogenetic disorder was found to be Philadelphia (+) in accordance with the literature.

In patients with ALL, the overall survival rate has been reported to be between 27 and 48% [10, 13]. Similarly, in our presented study, this rate was found to be 43.1%. It was observed in our study that the risk scoring at the time of diagnosis and the presence of cytogenetic anomaly did not have a significant effect on the rate of complete remission, and the immunophenotypic and morphological diagnosis did not affect the rates of achieving complete remission. This situation may be associated with the insufficient number of patients included in the study.

It was reported that gender, lymphadenomegaly, bone marrow blast rate, splenomegaly, and presence of mediastinal mass at the time of diagnosis were not effective in complete remission after treatment which was in line with our study [2, 3]. Consistent with the literature (complete remission rates have been reported to be between 74-93%), the rate of complete remission was observed as 72.7%. In studies, it has been shown that while the total survival rate is 5% in patients who cannot achieve complete remission, it increases to 45% in patients with complete remission [12]. It was shown in the current study that the total survival time was longer in patients with complete

Table 8. Determination of factors affecting overall survival				
	n	**Survival time (days)**	**%95 CI**	***p***
Hepatomegaly				
Exist	8	491 ± 81.57	331.14-650.89	0.799
None	36	530 ± 132.10	271.09-788.91	
Splenomegaly				
Exist	21	530 ± 89.53	354.52-705.48	0.715
None	23	603 ± 167.51	274.68-931.32	
Leukocyte count at diagnosis				
< 30,000 K/µL	25	661 ± 131.33	403.60-918.405	0.224
≥ 30,000 K/µL	19	426 ± 208.30	17.74-834.26	
Age				
< 35	27	603 ± 62.75	480-725	0.217
≥ 35	17	407 ± 263.76	0-923.96	
Cytogenetic Anomaly				
t(9;22) positive	6	100 ± 108.27	0-312.20	0.092
t(9;22) negative	38	603 ± 63.55	478.45-727.56	
Risk scoring				
Standard risk	6	661 ± 605.78	0-1848.33	0.929
High risk	38	527 ± 93.62	343.50-710.50	
Applied treatment regimen.				
HyperCVAD	33	603 ± 63.75	478.05-727.96	**0.009**
HyperCVAD + L-Asp	7	17 ± 4.90	7.40-26.60	
Complete remission				
No Remission	10	70.11 ± 20.42	30.08-110.14	***p* < 0.001**
Remission	32	1021.23 ± 174.72	678.77-1363.68	

L-Asp: L-Asparaginaz

Table 9. Determination of factors affecting disease-free survival				
	n	**Survival time (days)**	**%95 CI**	***p***
Hepatomegaly				
Exist	6	609 ± 132.11	350.07-867.93	0.424
None	25	359 ± 187.77	0-727.02	
Splenomegaly				
Exist	15	443 ± 153.67	141.80-744.20	0.181
None	16	567 ± 202.99	169.15-964.86	
Cytogenetic Anomaly				
t(9:22) positive	4	212.67 ± 69.67	76.12-349.24	0.167
None	27	772.57 ± 184.99	410-1135.15	

remission ($p < 0.001$).

In our study, in the HyperCVAD + L-asparaginase group, it was observed that the rates of treatment-related sepsis and treatment-induced excitus increased while the rates of achieving complete remission and total survival decreased.

CONCLUSION

It has seen that the general characteristics, response to treatment, and complications of adult ALL patients included in our study were similar to those in the literature. There is a need for new targeted treatment protocols for adult ALL patients with a total survival rate of up to 27%.

Authorship Contributions:

Conception: V.O., F.Ö., F.C. Design: V.O., F.Ö., F.C. Supervision: V.O., F.Ö. Funding: None, Data Collection or Processing: F.C., Analysis or Interpretation: V.O., F.Ö., F.C. Literature Review: F.C., V.O., N.K., Writer: F.C, V.O., N.K., Critical

Review: N.K.

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Conflict of Interest

No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

The incidence, risk factors and clinical outcome of pulmonary embolism in hospitalized patients with COVID-19

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ABSTRACT

Objectives: Coronavirus-19 disease can cause a wide spectrum of diseases. One of the major mortal complications of the disease is hypercoagulable state, including life-threatening pulmonary embolism. COVID-19 infections may predispose venous thromboembolism due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation. The aim of this study was to evaluate the incidence and risk factors for pulmonary embolism in hospitalized patients with COVID-19 in Turkey and to determine the impact of pulmonary embolism on clinical outcomes.

Results: 69 patients who were hospitalized for COVID-19 pneumonia between 15 March and 30 April 2020 and underwent CT angiography on clinical suspicion were included in the study. All patients received at least standard doses thromboprophylaxis. The incidence of the PE was 24.4% (n = 17). In patients with pulmonary embolism a higher frequency of males (88% vs 61%, p = 0.013), higher rates of smoking (75% vs 37% ,p = 0.008) and chronic renal failure (19% vs 4%,p = 0.04) were noted. Pulmonary embolism was positively correlated with heart rate > 100 bpm (r = 0.479, p < 0.001), more than two fold increase in D-dimer (r = 0.421,p < 0.001) and active smoking (r = 0.323, p = 0.008).In three patients with pulmonary embolism, intensive care, non-invasive mechanical ventilation and intubation was required, mortality occurred only in 1 (6.0%) patient.

Conclusion: In our study, the frequency of pulmonary embolism in the patient population infected with COVID-19 was found to be 24.4%, despite effective DVT prophylaxis. It should be kept in mind that pulmonary embolism is one of the most common complications in patients hospitalized for COVID-19 infection.

Thrombotic complications in patients diagnosed with COVID-19 are emerging as important sequelae that contribute to significant morbidity and mortality [1, 2]. Pulmonary embolism (PE), deep vein thrombosis, ischemic stroke and myocardial infarction are examples of complications described in patients with increasing frequency [1, 2]. A hypercoagulable state is a common abnormality in patients with COVID-19, and is due to infection, inflammation, hypoxia, immobilization, and diffuse intravascular coagulation with marked elevations seen in lactate dehydrogenase, ferritin, C-reactive protein, D-dimer and interleukin levels [3,4]. Concomitant pulmonary embolisms have been detected

on the computed tomography (CT) scans of patients hospitalized mainly for respiratory symptoms due to COVID-19 [5, 6]. The purpose of this study was to evaluate the incidence of COVID-19 patients that developed pulmonary embolism and compare their clinical characteristics and inflammatory markers, D-dimer values and outcomes.

METHODS

Study population

A total of 69 patients (49 males, 59.2 (15.8) years) diagnosed with COVID-19 pneumonia at our hospital from March 15 to April 30, who had computed tomography pulmonary angiogram (CTPA) due to deterioration in clinical status or sudden drop in oxygen saturation during their follow-up were retrospectively included in this study.

The local ethics committee of Bursa Uludag University Hospital approved this retrospective study and waived the need of informed consent.

Assessments

Data on patient demographics (age, gender), hospitalization status, comorbidities, treatments and laboratory and echocardiography findings were retrieved from the Picture Archiving and Communication System (PACS) database. Initial report validated by a pulmonary medicine specialist as well as axial images of all CT cases with iodine contrast media injection were reviewed by the same radiologist. Simplified pulmonary embolism severity index (PESI) scores were calculated based upon clinical variables.

Imaging

CTPAs were acquired on 64+ row scanners after injection of 50 to 75 ml of high concentration iodine contrast media, with the use of a bolus-tracking technique and a threshold of 160HU to 250HU in the main pulmonary artery. Tension was fixed at 100kV and automatic tube-current modulation was used, with a maximum mAs varying between scanners but always below 350mAs. When possible, patients were instructed to hold their breath and raise their arms above their head to minimize artifacts. Images were reconstructed with a slice-thickness of 1 mm in mediastinal and parenchymal windows, and transmitted to post-processing workstations for multiplane and maximum intensity projection reconstructions. When identified, acute pulmonary embolism was classified as truncal, lobar, segmental or sub-segmental based on the location of the most proximal luminal defect during the entire examination.

The diagnosis of COVID-19 was based on positivity of RT-PCR analysis for SARS-Cov-2 or on presence of typical CT findings (i.e. extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation) and compatible clinical data in RT-PCR-negative cases. Initial samples for RT-PCR analysis were obtained by nasopharyngeal swab, while a second or third sampling was required in some patients.

All patients in the study received a treatment protocol including hydroxychloroquine, azithromycin and prophylactic dose of low molecular weight heparin (LMWH).

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Chi-square ($\chi 2$) test was used for the comparison of categorical data, while independent sample t-test was used for analysis of the parametric variables. Pearson correlation analysis was used in the correlation analysis. Data were expressed as "mean ± standard deviation (SD), 95% confidence interval (CI) and percent (%) where appropriate. $p < 0.05$ was considered statistically significant

RESULTS

Baseline characteristics

The mean (SD) patient age was 59.2 ± 15.8 years and 49 of 69 patients were males. Of 69 patients diagnosed with COVID-19, 17(24.4%) had clinically relevant pulmonary embolism.

Pulmonary embolism was unilateral in (43.0%) cases and bilateral in 10 (57.0%) cases, while 9 patients had echocardiographically-confirmed pulmonary embolism findings (D-shape, increase in PAP), others had no serious pathological findings. When the radiological features of pulmonary embolism were analyzed, 35.7% were segmental, 14.3% were sub-segmental, 14.3% were truncal, and 35.7% were lobar.

Patient demographics and comorbidities in patients with vs. without pulmonary embolism

In patients with and without pulmonary embolism,

a significantly higher frequency of males (88% vs. 61%, p = 0.013) and higher rates of smoking (75% vs. 37%, p = 0.008) and chronic renal failure (19% vs. 4%, p = 0.049) were noted (Table 1).

No significant difference was noted in the mean age of patients with versus without pulmonary embolism (55.6 ± 18.1 vs. 60.1 ± 15.0 years, p > 0.05). COVID-19 positive patients with and without pulmonary embolism had similar rates of hypertension (25% vs. 24%), diabetes mellitus (19% vs. 16%), cardiovascular disease (19% vs. 18%), chronic heart failure (12% vs. 8%) (Table 1).

Laboratory findings in patients with vs. without pulmonary embolism

Troponin (36.8 ± 26.5 vs. 14.2 ± 20.8, p = 0.009) and ferritin (806.9 ± 683.2 vs 414.9 ± 419.8 ng/mL, p = 0.009) values were significantly higher in patients with vs. without pulmonary embolism. No significant difference was noted between the two groups in terms of other laboratory parameters, including D-dimer (2.38 ± 1.26 vs 4.13 ± 1.87) and CRP levels (65.7 ± 49.9 vs. 55.0 ± 42.3) (Table 2).

The risk of developing pulmonary embolism

Correlation analysis revealed that the likelihood of developing pulmonary embolism was positively correlated with heart rate of > 100 bpm (r = 0.479, p < 0.001), more than two-fold increase in D-dimer (r = 0.421, p < 0.001) and active smoking (r = 0.323, p = 0.008) (Table 3).

Table 1. Baseline characteristics in COVID-19 patients with vs. without pulmonary embolism

	COVID-19 patients (n = 69)		*p* value[1]
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Demographics			
Age (years), mean ± SD	55.6 ± 18.1	60.1 ± 15.0	NS[2]
Gender (male), n (%)	15 (88.0)	31(61.0)	**0.013**
Smoking, n (%)	12(75.0)	19(37.0)	**0.008**
Comorbidities, n (%)			
Hypertension	4(25.0)	12 (24.0)	NS
Diabetes mellitus	3(19.0)	8(16.0)	NS
Cardiovascular disease	3(19.0)	9(18.0)	NS
Chronic heart failure	4(12.0)	4(8.0)	NS
Chronic renal failure	3(19.0)	2(4.0)	**0.049**

NS: Not significant
[1]Chi square test, [1]t-test

Table 2. Laboratory findings in COVID-19 patients with vs. without pulmonary embolism

	COVID-19 patients (n = 69)		*p* value
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Laboratory findings, mean ± SD			
WBC (x1000/mm3)	5.07 ± 4.09	6.05 ± 4.18	NS
Hemoglobin (g/dL)	11.9 ± 3.7	10.3 ± 5.0	NS
Neutrophil (x1000/mm3)	4.9 ± 4.4	3.4 ± 2.9	NS
Lymphocyte (x1000/mm3)	1.3 ± 0.9	0.8 ± 0.6	NS
Glucose (mg/dL)	144.7 ± 43.3	130.0 ± 43.9	NS
GFR (mL/sec)	64.7 ± 35.5	67.6 ± 37.6	NS
AST (U/L)	23.5 ± 5.3	12.2 ± 4.7	**0.017**
ALT (U/L)	32.3 ± 24.4	36.0 ± 29.7	NS
Sodium (mmol/L)	137.6 ± 4.2	137.6 ± 3.2	NS
CRP (mg/ml)	65.7 ± 49.9	55.0 ± 42.3	NS
D-dimer (ng/mL)	2.38 ± 1.26	4.13 ± 1.87	NS
Ferritin (ng/ml)	806.9 ± 683.2	414.9 ± 419.8	**0.009**
Troponin	36.8 ± 29.5	14.2 ± 20.8	**0.009**

WBC: White blood cell; GFR: Glomerular filtration rate; AST: Aspartate aminotransaminase; ALT: Alanine aminotransaminase; CRP:C-reactive protein, NS: Not significant; t-test

Table 3. Correlation between pulmonary embolism and study parameters		
Variables		**Development of pulmonary embolism**
> 2-fold increase in D-dimer	N	69
	r	0.421
	p	**< 0.001**
Smoking	N	69
	r	0.323
	p	**0.008**
Heart rate > 100 bpm	N	69
	r	0.479
	p	**< 0.001**
Pearson correlation analysis, r: correlation coefficient		

Clinical outcomes in patients with vs. without pulmonary embolism

In three patients with pulmonary embolism, intensive care, non-invasive mechanical ventilation or intubation was required, while none of them died. In the group without pulmonary embolism, 2 patients had intubation need due to respiratory failure associated with ARDS and died (Table 4).

Accordingly, amongst the COVID-19 patients with pulmonary embolism, mortality occurred only in 1(6.0%) patient, due to massive pulmonary embolism and respiratory failure. In those without pulmonary embolism, 2(4.0%) patients died from respiratory failure due to ARDS. No significant difference was noted in mortality rates of COVID-19 patients with and without pulmonary embolism (6.0% vs. 4.0%, p > 0.05) (Table 4).

DISCUSSION

Our findings revealed the likelihood of developing pulmonary embolism among COVID-19 patients to be 24.4% (17/69) over a one-month period. This is in line with data from recent studies on the rates of pulmonary embolism (range, 23-30%) in COVID-19 patients who had CTPA in their follow up [7-9].

The remarkably high rates of pulmonary embolism in the current study, exceeding the rates reported in patients without COVID-19 infection, seems to indicate the association of COVID-19 with an increased risk of pulmonary embolism. In epidemiological studies, annual incidence rates for pulmonary embolism were reported to range from 39-115 per 100 000 population and for DVT to range from 53-162 per 100 000 population [10]. The frequency and severity of venous thromboembolic events are largely determined by genetic or acquired factors. Given that the presence of potential risk factors such as malignancy and previous surgical operations were amongst the exclusion criteria of the current study, it is noteworthy that the observed incidence was quite high. Indeed, high incidence of pulmonary embolism in COVID-19 patients in the literature has been considered to indicate an association between COVID-19 and venous thromboembolic disease [3, 11, 12].

Based on clinical studies, pulmonary embolism is considered to occur at 60 to 70 years of age in majority of cases, while autopsy data indicate the association of 70 to 80 years of age with the highest incidence [13]. In the current study, the mean age of total population was be 59.2(SD 15.8) years along with no significant difference in patients with vs. without pulmonary embolism in terms of age. The high rates of pulmonary embolism in a population without major risk factors seems to indicate the likelihood of COVID-19 per se to predispose development of venous thromboembolism, similar to activation of the coagulation system reported in other virus infections [14, 15]. In particular, coronavirus infections may trigger venous thromboembolism through participation of multiple pathogenic mechanisms such as endothelial

Table 4. Clinical outcomes in COVID-19 patients with vs. without pulmonary embolism			
	COVID-19 patients (n = 69)		***p* value**
	Pulmonary embolism (+) (n = 17)	**Pulmonary embolism (-) (n = 52)**	
Clinical outcomes, n(%)			
ICU stay	3 (16.0)	2(4.0)	NS
Mechanical ventilation need	2(12.0)	2(4.0)	NS
ARDS	0(0.0)	2 (0.04)	NS
CPAP need	1(6.0)	1(2.0)	NS
Mortality	1 (6.0)	2(4.0)	NS
ICU: Intensive care unit; ARDS: Adult respiratory distress syndrome; CPAP: Continuous Positive Airway Pressure; NS: Not significant [1]Chi square test			

dysfunction, characterized by increased levels of von Willebrand factor; systemic inflammation, by Toll-like receptor activation; and a procoagulant state, by tissue factor pathway activation [16]. In a subgroup of patients with severe COVID-19, high plasma levels of pro-inflammatory cytokines were reported [17]. The direct activation of the coagulation cascade by a cytokine storm is also possible. The development of severe hypoxemia in some patients with COVID-19 seems also notable given the evidence on facilitation of thrombus formation under hypoxic conditions as reported both in animal models of thrombosis and in humans [18]. The vascular response to hypoxia is controlled primarily by the hypoxia-inducible transcription factors, whose target genes include several factors that regulate thrombus formation [19]. Moreover, the indirect causes, such as immune-mediated damage by antiphospholipid antibodies, may partially contribute, as speculated by Zhang et al. [20]. However, our study revealed no findings supporting the immune-mediated damage.

Notably, our findings revealed no significant impact of concomitant pulmonary embolism on mortality rates in patients with COVID-19. In non-COVID-19 patient populations, mortality from acute pulmonary embolism has been reported to be as high as 30% if untreated, whereas to be 8% in diagnosed and treated cases [13]. Hence, in patients with COVID-19 mortality rates from pulmonary embolism seems to be lower than expected in other patient populations. This may be explained by the fact that all COVID-19 patients were hospitalized patients who were already receiving LMWH at prophylactic doses. A recent study reported that LMWH or unfractionated heparin (UFH) at prophylactic doses were associated with a reduced 28-day mortality in more severe COVID-19 patients displaying a sepsis-induced coagulopathy (SIC) score ≥ 4 (40.0% vs 64.2%, $p = 0.029$) or D-dimer levels > 6-fold higher than the upper limit of normal (32.8% vs 52.4%, $p = 0.017$) [21, 22]. In addition, administration of hydroxychloroquine sulfate in all of our patients may also have a beneficial effect, given that hydroxychloroquine sulfate was reported to be associated with reduction in incidence of fatal pulmonary embolism and venous thromboembolism in some studies (23-26). Hydroxychloroquine was also reported to reduce the red blood cell aggregation without prolonging the bleeding time along with a variably demonstrable reduction in platelet aggregation and blood viscosity in humans, while to reduce the thrombus size in experimental models [26].

In contrast the other studies, initial D-dimer values were high but similar in patients with and without pulmonary embolism in our study [9, 12, 27]. Although there was no significant difference between the two groups in terms of initial D-dimer values, the likelihood of more than 2-fold increase in D-dimer values from baseline was significantly higher in patients with pulmonary embolism. High values of D-dimer may be related to a higher activation of blood coagulation in COVID-19 patients secondary to a systemic inflammatory response syndrome or as a direct consequence of the SARS-CoV-2 itself. Features of disseminated intravascular coagulation (DIC) and pulmonary embolism, such as increase in D-dimer levels and fibrin degradation products, are highly prevalent in COVID-19 [28]. In a retrospective cohort study, elevated D-dimer levels (>1 g/L) were reported to be strongly associated with in-hospital mortality, and this relationship was maintained in multivariate analysis (OR 18.4, 95% CI 2.6–128.6; $p = 0.003$) [29]. Elevated D-dimer level on admission was not a significant determinant of pulmonary embolism in our cases. This may be related to the fact that D-dimer acts as an acute phase reactant in COVID-19. Therefore, continued D-dimer monitoring in patients may be important in predicting pulmonary embolism in COVID-19 infection.

Similar to previously reported distribution characteristics of pulmonary embolism in COVID-19 patients, most of pulmonary embolism cases were classified as segmental and sub-segmental in the current study [7]. Notably, in pulmonary embolism studies among patients without COVID-19, the location of embolus was generally reported to be proximal [30-32].

Chronic renal failure, male sex and smoking were risk factors for development of pulmonary embolism in the current study. Chronic diseases and heavy smoking are also risk factors of venous thromboembolism for normal population [33, 34]. In chronic kidney disease patients, mechanisms contributing to a pro-coagulant state include increased tissue factor, vWf, factor XIIa, VIIa, and fibrinogen levels along with reduced tissue plasminogen activator [35]. Data are conflicting as to whether male sex is a risk factor for pulmonary embolism; however, an analysis of national mortality data reported 20-30% higher mortality risk from pulmonary embolism among men than among women [36].

In approximately 16% of cases with pulmonary embolism, a transfer to ICU was required and need

for mechanical ventilator support was evident in two of these patients. No significant difference was noted in need for ICU stay or mechanical ventilator support, as well as in mortality rates between patients with and without pulmonary embolism. In contrast, a recently published study indicated the association of pulmonary embolism with increased risk of ICU admission and mechanical ventilation in COVID-19 patients [6]. This discrepancy may also be related to use of prophylactic doses LMWH and hydroxychloroquine sulfate in all of our patients.

Certain limitations to this study should be considered. First, we did not evaluate antithrombin 3, Protein C, S, and anticardiolipin antibody levels in each patient. Second, given that all patients were receiving prophylaxis in terms of venous thromboembolism, our findings may not reflect the incidence of pulmonary embolism in non-hospitalized COVID-19 patients.

CONCLUSION

In conclusion, approximately 24.4% of COVID-19 patients in the current study were diagnosed with pulmonary embolism, despite effective DVT prophylaxis. Development of pulmonary embolism seems not to affect mortality in COVID-19 patients who were under effective DVT prophylaxis. Therefore, use of contrast-enhanced thorax CT in monitoring of COVID-19 patients with low saturation seems to be a useful follow-up strategy, regardless of the risk factor status. It should be investigated whether the condition due to disease progression or comorbid pulmonary embolism, given that these patients can recover after effective treatment.

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ORIGINAL ARTICLE

A Comparative Study of the Varying Effects of Acetylsalicylic Acid on Thromboxane B2

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ABSTRACT

Objectives: In this study, we evaluated the antiaggregant efficacy of the standard dose ASA and very low doses of ASA, which we use in the clinic, by looking at the serum thrombocyte B2 level and investigated the difference between the two groups.
Method: The study was built on 20 mg (1/4), 40 mg (1/2), 80mg 1/1 of Babypirin and 150 mg (1/2) of Dispril doses. 10 patients were grouped for each one of the four prescribed doses. Those patients with a history of gastrointestinal bleeding, peptic ulcer, hematological disorders, bronchial asthma, chronic obstructive pulmonary disease and allergy to ASA were excluded from the study. ASA doses were administered once a day. Before ASA, blood was collected from all patients for serum thromboxane (Tx) B2 analysis. Then, after 14 days of ASA use, blood was drawn from the patients again for the second time to detect TxB2 decrease.
Results: There was no significant difference between the groups in terms of age and gender ($p>0.05$). There was a significant difference between the groups in terms of % decrease in TxB2 after treatment ($p=0001$). In the post hoc test, it was concluded that the % decrease in the 20mg group was significantly lower than the other three groups ($p=0.002$), and the % decrease between the 40,80 and 150mg groups was higher in all three groups compared to the 20mg group. On the other hand, there was no difference in % reduction in the 40,80 and 150 mg groups ($p>0.05$).
Conclusion: The use of low-dose ASA seems to be more beneficial when considered in all aspects. Our results are that there is no difference in doses up to 40mg when considered from the antithrombotic point of view.

Acetylsalicylic acid (ASA) is arguably one of the most important pharmaceutical agents based on its widespread use and employment in various disorders. Besides its classic anti-inflammatory efficacy, it has a positive selective and proven effect on cardiovascular mortality via its anti-aggregating ability. The most prevalent usage avoidance is due to dose dependent gastrointestinal side effects and inhibition of prostacyclin.

In this study, we evaluated the antiaggregant efficacy of the standard dose ASA and very low doses of ASA, which we use in the clinic, by looking at the serum thrombocyte B2 level and investigated the difference between the two groups.

METHODS

The study was conducted on outpatients who had come to the general internal

medicine and diabetes clinic due to complaints of coronary artery disease and hospitalized at the second internal medicine clinic of Şişli Etfal Hospital. Babypin® 80 mg (Pfizer) and Dispril ® 300 mg pharmaceutical products were used as ASA. The study was built on 20 mg (1/4), 40 mg (1/2), 80mg 1/1 of Babypirin and 150 mg (1/2) of Dispril doses. 10 patients were grouped for each one of the four prescribed doses.

Those patients with a history of gastrointestinal bleeding, peptic ulcer, hematological disorders, bronchial asthma, chronic obstructive pulmonary disease and allergy to ASA were excluded from the study. ASA doses were administered once a day.

Measurement of serum thromboxane B2:

Blood samples were drawn from all patients in order to assess serum thromboxane B2 levels prior to administering ASA. Following 14 days of ASA usage, blood samples were drawn once again to determine whether thromboxane B2 levels had fallen. Blood samples were centrifuged right away and after serum was obtained specimens were kept at -24C. All serum samples were analyzed together at the end of the study. TBX2 levels were determined by ELİSA using acetylcholinesterase and ELİMAN reactive. This particular test functions on free and bound (bound to acetylcholinesterase) TXB2 competing. Eliman reactive (contains acetylcholinesterase substrate) which was added into the medium after the administration of rabbit antiserum; rendered a yellow tinge whose optical density was measured at 412 manometers by using spectrophotometry to assess each individual level.

Statistical Analysis

Statistical analysis were executed by using the SPSS (Statistical package for social sciences) programme. Deviation level was taken as 0.005 in intergroup comparisons. ANOVA (single direction variation analysis) was employed in normally dispersed variables; single Kruskal-Wallis's test was employed in non-normally dispersed variables. When a difference was detected, meaningfulness level border was moved to 0.0008. Mean-Whitney U test was applied as a post-hoc test. ki square test was employed to evaluate groups sexually.

RESULTS

There was no meaningful difference amongst groups related to age or sex ($p>0.005$). It can be summed up that with reference to the decrease in TbX2 in terms of percentage; meaningful differences were detected amongst groups. Based on the post hoc test, the decrease in terms of percentage in the group that received 20 mg. was meaningfully low compared with the other 3 groups ($p=0.002$). The decrease in terms of percentage with reference to the groups that received doses of 40 mg., 80 mg., 150 mg., was higher compared with the group that received the 20 mg. dose. It was also assessed that there was no difference in the decrease amongst the 40 mg., 80 mg., 150 mg. dose group (Table 1, 2, 3 and 4).

Table 1. TxA2 change in the group using 20 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
40	FEMALE	16,6	277-231
64	FEMALE	13,2	347-301
64	FEMALE	14,9	401-341
54	FEMALE	12,8	311-271
43	MALE	14,7	306-261
50	MALE	11,8	296-261
67	MALE	20,6	402-319
51	MALE	18,2	296-242
55	MALE	12,6	309-270
70	FEMALE	12,7	321-280

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

DISCUSSION

ASA is a selective antithrombotic agent in stopping thrombus formation in coronary artery disease and cerebrovascular diseases both in acute and in chronic cases. Data obtained from antiplatelet remedial studies have shown that daily doses <160 mg; 160mg to 325 mg., 500 mg to 1500 mg. of ASA have similar benefits [1]. Latest guidelines recommend 30 mg to 100 mg of ASA to avoid non cardioembolic secondary ischemia based on similar benefits no matter how high the dose is and to avoid GİS complications with increasing dose. According to American College of chest Physicians` 2012 guideline, the recommended dose of ASA is 75-100 mg /day [2] :according to the American Heart Association/American Stroke Association's 2021 guideline the recommended dose of ASA is 50-325 mg/day.[3]

The optimal daily dose of ASA to avoid long duration secondary cardiovascular incidents is indeterminate. The prevalently prescribed doses are 81 mg. and 100 mg. Many studies and their meta-analyses have evaluated 75 mg. t0 1300 mg./day of ASA. The Union of Anti Thrombus Studies has shown through meta-analyses of the above-mentioned studies that ASA doses of 76 mg. to 1300 mg. render similar benefits [4]. Nevertheless, it has been proven that GİS bleeding risk increases with doses exceeding 325 mg/day.

ASA inhibits COX and thus causes a decrease in the formation of TxA2. It causes prostacyclin not to come into being by inhibiting the same enzyme. TxA2 is a strong vasoconstrictor that increases thrombocyte aggregation; whereas prostacyclin is a strong anti-

Table 2. TxA2 change in the group using 40 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
55	MALE	43,2	344-196
65	FEMALE	70,4	392-116
70	FEMALE	44,6	327-181
60	FEMALE	26,9	412-301
70	MALE	26,3	288-212
48	FEMALE	22,9	401-309
64	MALE	36	300-192
55	FEMALE	36,3	316-201
63	MALE	29	386-274
47	MALE	29,2	421-298

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

Table 3. TxA2 change in the group using 80 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
32	MALE	55,0	329-148
58	FEMALE	40,7	336-199
56	FEMALE	30,8	266-184
27	FEMALE	31,3	287-197
28	FEMALE	27,6	336-243
55	FEMALE	25,5	290-216
50	FEMALE	26,5	328-241
60	MALE	38,9	272-166
56	MALE	39,8	321-193
50	MALE	34,7	308-201

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

Table 4. TxA2 change in the group using 150 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
50	FEMALE	33,1	287-192
29	FEMALE	35,5	304-196
28	MALE	34,3	329-216
31	MALE	38,2	329-203
75	MALE	34,1	290-191
59	FEMALE	31,6	306-209
48	FEMALE	49,6	281-142
64	FEMALE	37,3	321-201
50	MALE	34,4	308-202
61	MALE	37,7	307-191

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

aggregating agent and vasodilator which means that it functions antagonistically.

Besides inhibiting platelets, ASA inhibits COX in vascular tissue which in turn causes prostacyclin to be inhibited.[5]. The important question that we should ask at this point is: whether ASA is more effective in inhibiting COX in thrombocytes or in vascular tissue. Are such effects dose dependent and variable? Do such effects alter the balance between TXA2 and prostacyclin. İn case ASA's inhibiting effect is more pronounced than its inhibiting effect on TXA2; ASA could actually cause more thrombus to come into being.

Once ASA inhibits COX in thrombocytes, it emerges as an irreversible effect and thrombocytes cannot synthesize COX anymore throughout their life span. Vascular tissue on the contrary has the ability to re-synthesize COX after being exposed to ASA. [6]

In a study conducted on coronary bypass patients; both arterial and venous prostacyclin &TxB2 levels were screened prior to ASA exposure and after 80mh to 325 mg of ASA exposure.

80 mg. of ASA rendered 83% decrease in venous prostacyclin; 40 mg. of ASA caused 35% decrease in arterial prostacyclin whereas the decrease was 71% with 325 mg. of ASA [7, 8].

It has been argued in some other studies that ASA doses lower than 100 mg. were not effective in inhibiting thrombocytes from aggregating and in prostacyclin being synthesized [9, 10]. In another study in comparison with a dose of 75 mg of ASA; as low as 20 mg of ASA was claimed to have inhibited thrombocyte TxA2 secretion and aggregation. [11]. We have found out that doses of 40 mg of ASA & over rendered 40% decrease in TxB2; 20 mg of ASA rendered less than 15% decrease in TxB2 in our study.

ASA's arguably most important clinical setback consists of GIS side effects: bleeding, gastric or duodenal ulcers [12]. Such GIS side effects are of paramount importance due to the fact that once a patient experiences any one of them; neither the doctor nor the patient wishes to continue using ASA. As a result, the employment of an effective anti-thrombus agent gets lost. It is also a possibility that catastrophic intracranial bleedings can happen. According to 2019 meta-analyses incorporating ASCEND, ARRİVE, ASPREE clinical studies; low dose ASA intake (<100 mg/day) increased the risk of intracranial bleeding compared with placebo. [13]. It yet has not been clearly delineated, which dose window renders ideal antithrombotic effect to zero GIS side effects and bleeding complications.

Results of our study have shown similar outcomes with most other studies related to the topic. Nevertheless, some studies have results pointing to significant decrease in TxB2 with relatively low doses of ASA. Those studies with very low doses were conducted on healthy volunteers who didn't use any other medicine. Patients who were enrolled in our study used a number of pharmaceuticals each and drug interactions might have caused absorption related issues.

CONCLUSION

In conclusion, approximately 24.4% of COVID-19 patThe base of our study was to outline the effects of

ASA (with varying doses) on thromboxane synthesis. Studies with low doses of ASA have proven that thromboxane synthesis inhibition was dose correlated. Lower dose usage of ASA seems to be more beneficial when all effects are taken into consideration. Our results have proven that antithrombotic effects of ASA are stable and remains constant up to 40 mg.

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Conception: O.O., Design: O.O., Supervision: S.C., A.Y., Funding: - Data Collection or Processing: O.O., S.C., Analysis or Interpretation: O.O., S.C., Literature Review: O.O., S.C., A.Y., Writer: O.O, S.C., A.Y., Critical Review: A.,Y.

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CASE REPORT

Adult Gitelman Syndrome: Case Report and Review of the Literature

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ABSTRACT

Gitelman Syndrome, the most frequently detected hereditary tubulopathy in adults, was first described by Gitelman et al. in 1966 in 3 adults who presented with tetany associated with hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The estimated prevalence of Gitelman syndrome, which is considered as a variant of Bartter syndrome with autosomal recessive inheritance, is reported as 1:40,000. In this article, a case diagnosed with Gitelman Syndrome, who was hospitalized many times, including the intensive care unit, with symptoms such as constipation, weakness, nausea and vomiting since childhood is presented.

One of the most prevalent inherited renal tubular diseases is known as Gitelman syndrome (GS), which is brought on by mutations that inactivates located on chromosome 16(16q13) in the SLC12A3 gene, which codes for the sodium chloride cotransporter (NCC) that is expressed in the apical membrane of distal convoluted tubule (DCT) cells and is thiazide sensitive. Gitelman variant of Bartter syndrome is seen in adolescence and adulthood and often has a milder clinical course than Bartter Syndrome. Although the cases are generally asymptomatic, symptoms such as fatigue, muscle weakness, cramps, tetany, fatigue, nocturia and polydipsia are common. Polyuria and nocturia are common due to nephrogenic diabetes insipidus due to hypokalemia. Growth retardation is also common in these cases.

CASE REPORT

A 28-year-old female patient was hospitalized for further examination and evaluation after her application to the emergency department due to increased complaints of fatigue, nausea and vomiting, which she stated for about 10 years. The patient, who did not have any known additional disease and no medication that she used constantly, stated that she had constipation and oral intake disorder throughout her life, and that her vomiting had increased especially in the last 4-5 days. The patient, who stated that he had a history of intensive care hospitalization 3 months ago with similar complaints, had sinus rhythm in electrocardiography, his QT interval was normal, and no significant U wave was observed. In the renal ultrasound, the parenchymal

echo was reported as bilateral grade I-II increased, while the parenchymal echo was normal in the thyroid ultrasound, no nodules and pathological lymphadenopathy were observed.

In laboratory evaluation, Ca = 8.0 mg/dL, p = 1.9 mg/dL, K = 1.8 mg/dL, Na = 128 mg/dL, Creatinine = 0.46 mg/dL, Mg = 1.52 mg/ dL was observed as Parathormone (PTH) = 32.3 mU/L, while pH = 7.58, pCO2 = 71.9 and HCO3 = 67.9 in blood gas. Autoimmune markers p-anca, c-anca and Anti-dsDNA tests, and hormone levels such as Cortisol, FSH, LH, prolactin, Anti-TPO, Anti-TG and Thyroglobulin were reported within normal limits. 24-hour urine Na = 27.6 mmol, Ca= 47.64 mg, and Cl = 20.39 mmol.

In the case, the patient was diagnosed with Gitelman Syndrome, in spite of the existing cachexia, with normal breast development, genital hair growth, no growth retardation, the characteristic phenotype of Bartter Syndrome (triangular face, large eyes), and the dramatic improvement of his complaints with the potassium and magnesium treatment given. After IV replacements, oral magnesium potassium preparations and PPI were prescribed, and she was discharged.

DISCUSSION

The diagnosis of Gitelman syndrome is mainly based on clinical, biochemical and molecular findings. The disease is often confused with Bartter syndrome. Gitelman syndrome is distinguished from Bartter syndrome by the milder clinical presentation, absence of polyuria, normal or slightly decreased tubular concentration ability, decreased urinary calcium excretion, decreased serum magnesium, and absence of maternal polyhydramnios or prematuration [1-3]. Although chondrocalcinosis is rarely seen in Gitelman syndrome, it is not seen in Bartter syndrome. In addition, rare arrhythmias due to electrolyte imbalance may occur. Chronic hypomagnesemia has been blamed for the development of chondrocalcinosis in a small number of patients. Persistent hypomagnesemia suppresses PTH secretion and may cause chondrocalcinosis by impairing the function of enzymes such as alkaline phosphatase, which regulates pyrophosphate concentration in the extracellular space [4].

Progression to chronic renal disease is rare and few cases have been reported so far. Blood pressure is usually normal. Urinary potassium and magnesium excretion is decreased. Urinary calcium is usually below 2 mg/kg. Renal functions, urinary PgE2 and cAMP are normal. Thiazide diuretics similarly suppress the Na/Cl cotransporter in the distal tube. All findings seen with long-term thiazide use are similar to those found in Gitelman's Syndrome [5]. However, hypomagnesemia, which is an important finding in Gitelman Syndrome, is rarely seen in thiazide use. Despite all clinical and laboratory findings, it is often difficult to diagnose and differentially diagnose Bartter Syndrome and Gitelman Syndrome. Molecular genetic studies have made significant progress in the differential diagnosis of these syndromes [1].

Differential diagnosis

In the differential diagnosis, especially Bartter syndrome (type 3), use of diuretics and laxatives, and chronic vomiting should be considered [1]. Rarely, cisplatin use and autoimmune diseases may also cause Gitelman syndrome-like findings. Diuretic and laxative use, chronic vomiting can be detected with a careful history taking and physical examination.

Treatment

The cases are usually asymptomatic and do not require treatment. The long-term prognosis is good. The goal of treatment is to correct electrolyte abnormalities and symptoms [6]. In these patients, it is possible to improve the quality of life with magnesium replacement. With regular magnesium treatment, hypomagnesemia, hypokalemia and hypocalciuria improve, tetany and acid-base imbalance are prevented. Magnesium chloride, magnesium aspartate or magnesium lactate salts are divided into 3-4 parts per day and given in a total dose of 4-5 mg/kg/day. Hypomagnesemia may occur as a result of urinary potassium loss. Potassium requirement may be as high as 10 mg/kg/day [5]. In general, MgCl is preferred because of chlorine loss. A high salt diet is recommended. The tendency to chondrocalcinosis is also controlled with magnesium therapy. Diarrhea is the most common side effect of magnesium replacement. Potassium and prostaglandin suppressors are generally not needed, but some patients may require potassium replacement. Aldosterone antagonists (amiloride and spironolactone) can be used to correct the serum potassium level. In potassium deficiency, hypokalemia may be resistant to replacement with potassium salts, in which case it is important to replace magnesium first [5, 6].

CONCLUSION

Patients with fatigue, weakness, muscle pain and cramps should be evaluated for electrolyte imbalance, and patients with hypomagnesemia and hypocalciuria should be investigated for Gittelman Syndrome.

Authorship Contributions

Conception: DSC., NK., F.İ. Design: DSC., F.i., N.K. Supervision: NK Funding: None, Data Collection or Processing: DSC., Fİ. Analysis or Interpretation: DSC., F.İ., N.K. Literature Review: DSC., F.İ, N.K., Writer: DSC., N.K. Critical Review: N.K.

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Conflict of Interest

No conflict of interest was declared by the authors.

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