2024-VOLUME: 1 ISSUE: 1

CERASUS JOURNAL OF MEDICINE

CJM

ISSN

GİRESUN TRAINING AND RESEARCH HOSPITAL

CERASUS JOURNAL OF MEDICINE

CERASUS JOURNAL OF MEDICINE

VOL 1, NO 1, 2024

Journal title abbreviation is “Cerasus J Med”.

Aksu Mahallesi Mehmet İzmen Caddesi No.145 Merkez/Giresun/Türkiye

https://giresuneah.saglik.gov.tr/

https://dergipark.org.tr/en/pub/cjm/

cerasusjournalofmedicine@gmail.com

CJM
CERASUS
JOURNAL OF MEDICINE

Journal Boards

CJM
CERASUS
JOURNAL OF MEDICINE

CJM
CERASUS
JOURNAL OF MEDICINE

CJM
CERASUS
JOURNAL OF MEDICINE

Nurçe Çilesizoğlu Yavuz, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Demet Sengul, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Isıl Deniz Oğuz, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Devrim Bektaş, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Seyhan Yılmaz, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Kürsad Aytekin, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Meltem Arzu Yetkin, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Tülin Akagün, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Zeki Günaydın, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Serdar Aslan, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Berkan Şahin, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

Hasan Mücahit Özbaş, MD
Giresun University, Faculty of Medicine, Giresun, Türkiye

CJM
CERASUS
JOURNAL OF MEDICINE

CJM
CERASUS
JOURNAL OF MEDICINE

CONTENTS

CJM
CERASUS
JOURNAL OF MEDICINE

EDITORIAL

Since its opening, 'Giresun Training and Research Hospital,' making significant progress, takes pride and joy in presenting the academic journal named Cerasus Journal of Medicine (CJM) to our esteemed readers. Our journal will be published in English in the field of medical sciences every January, May, and September of each year. All submissions sent to our journal for publication will undergo a double-blind peer-review process, and if deemed scientifically adequate, they will earn the right to be published.

As CJM, I would like to express my gratitude to the Dergipark administrators and technical support team for their valuable contributions during the formation and publication process of our journal. I personally thank our colleagues, who took the first steps with us towards open-access scientific publishing in the Editorial Board, for their dedicated work. I extend our thanks to our esteemed colleagues who accepted our invitation to be part of the Editorial Board and carried out the reviewing process with great care.I see these meticulous contributions and the demonstrated precision as a guarantee of the scientific level CJM will achieve.

We hope to become a journal indexed in national and international databases, including the TR-DİZİN, in the shortest time possible, and we look forward to the support of our valued readers. With the contributions of esteemed academics, we aim to achieve greater and more beautiful accomplishments and take our journal to the best possible places.

Best regards…
Fazıl Kulaklı

CERASUS JOURNAL OF MEDICINE

REVIEW ARTICLE

The relationship between autism spectrum disorder, gut-brain axis and gut microbiota

Gülsüm YİTİK TONKAZ[1]
Bedia Sultan ÖNAL[2]
Ertuğrul ÇAKIR[3]

1. *Child and Adolescent Psychiatry Clinic, Giresun Maternity and Children Training and Research Hospital, Giresun, Turkey, gulsumyitik@gmail.com*

2. *Department of Child and Adolescent Psychiatry, Giresun University, Faculty of Medicine, Giresun, Turkiye, onalbediasultan@gmail.com*

3. *Department of Radiology, Giresun University, Faculty of Medicine, Giresun, Turkey drcakir@outlook.com*

Received: 9 December 2023
Accepted: 2 January 2024
Published: 31 January 2024

Corresponding Author: Gülsüm YİTİK TONKAZ, ORCID ID: 0000-0001-7195-2293

Child and Adolescent Psychiatry Clinic, Giresun Maternity and Children Training and Research Hospital, Giresun, Turkey,

E-mail: gulsumyitik@gmail.com

Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder in which symptoms such as difficulty in social interaction, communication problems, limited interests, and limited behavioral patterns are observed. The prevalence of ASD has been increasing over the years, but its etiology has not been fully elucidated. Gastrointestinal (GI) symptoms are a common comorbidity in children with ASD, but the underlying mechanisms are unknown. Many studies have shown alterations in the composition of the gut microbiota and their metabolic products in patients with ASD. The gut microbiota influences brain development and behaviors through the neuroendocrine, neuroimmune, and autonomic nervous systems. In addition, abnormal gut microbiota is associated with several diseases, such as obesity, diabetes, autoimmune diseases, neurodegenerative diseases, and psychiatric diseases (ASD, depression, anxiety disorder, etc.). In this review, we aim to provide information about the bidirectional interactions between the central nervous system and the gastrointestinal tract (the gut-brain axis), the possible roles of the gut-brain axis and gut microbiota in the etiology of autism spectrum disorder, and current hypotheses.

Keywords: Autism spectrum disorder, Gut Microbiota, Gut-Brain axis

Introduction

Autism Spectrum Disorder (ASD) is a childhood neurodevelopmental disorder characterized by social and communicative deficits, repetitive and stereotyped behaviors, and limited interests [1]. The prevalence of this disorder which is gradually increasing today, was determined as 2.76% (1/36) according to 2020 data [2]. In the same study, it was also reported that ASD is 3.8 times more common in boys than in girls [2].

You may cite this article as: Yitik Tonkaz G, Önal BS, Çakır E. The relationship between autism spectrum disorder, gut-brain axis, and gut microbiota. *Cerasus J Med*. 2024;1(1):1-11.

The etiology of autism, characterized by a wide spectrum of clinical symptoms, is not yet fully known.

Studies have shown that children with ASD are frequently accompanied by gastrointestinal symptoms such as food intolerance, chronic constipation, nausea, vomiting, chronic diarrhea, gastroesophageal reflux, bloating, and indigestion, with rates ranging from 46% to 84 % [3]. It has also been reported that these symptoms may be related to the degree of deficits in social relationships, the severity of stereotypic behaviors, hyperactivity, and aggression in children with ASD [4]. The detection of these comorbid conditions and the determination of the relationship between certain neuropsychiatric disorders and the gastrointestinal system have brought attention to the investigation of the 'Gut-Brain Axis' in the etiology of autism.

The 'Gut-Brain axis' is a dynamic and bidirectional structure that includes many tissues and organs such as the brain, secretory glands, intestine, immune cells, and intestinal bacterial flora. It is suggested that the exchange of signals and information along this axis affects the chemical structure and behavior [5]. The vagal nerve, including sympathetic and parasympathetic branches of the autonomic nervous system; the bacterial cell wall, which activates the immune system and neuroendocrine pathways; tryptophan and short-chain fatty acids, metabolites of intestinal bacteria; neurotransmitters and neuropeptides are important communication tools of this axis [5].

In this review, we aim to provide information about the possible roles of the gut-brain axis and gut microbiota in the etiology of autism spectrum disorder and current hypotheses.

1. Gut Microbiota

The intestinal bacterial flora (gut microbiota), which contains millions of species and about 10^{14} microorganisms, was defined as microbiota in 2007 by the Human Microbiome Project (HMP) [6]. The number of these microorganisms colonizing various parts of the body, such as the skin, genitals, and intestines, is known to be about ten times greater than the number of cells in the human body. *Firmicutes* and *Bacteriodetes* bacterial families are predominant in this microbial structure, which shows different distributions in the gastrointestinal tract due to physiological and chemical properties. In addition to bacteria, this microbial diversity also includes eukaryotes, viruses, bacteriophages, and different families of fungi [6].

The gut microbiota, which begins to develop within a very short time after birth, is thought to affect human health directly or indirectly [7]. Studies have shown that the gut microbiota act as a barrier that prevents the proliferation of pathogenic organisms, contributes to the digestion of food, and degradation of toxic and waste substances, and plays an important role in the regulation of lipid and glucose metabolism, activation of the immune system and gene expression. Along with these functions, metabolites produced by the gut microbiota and released into the peripheral circulation have been reported to contribute to the development and function of the central nervous system [8].

The number and content of the gut microbiota, a symbiotic life with the human host, is affected by many factors such as age, genetics, dietary habits, geographical region, mode of birth, gestation period, antibiotic, pre-biotic or probiotic use [9]. The alteration or disruption of this system, which is normally in equilibrium, for any reason is defined as dysbiosis. This condition, which is closely related to immune dysregulation, is thought to lead to serious metabolic and inflammatory pathologies and predispose to many diseases [10].

2. The Gut-Brain Axis

Microbiology and psychiatry sciences, which have developed in different fields for many years, have started to be investigated together with the progress of metagenomic studies and the development of 16s ribosomal RNA sequence analysis methods. Research has shown that gut microbiota, whose species and number can be determined with developing methods, is effective in many physiological events such as digestion, growth, immune system, and body energy balance (homeostasis) [10]. The gastrointestinal tract contains the enteric nervous system, composed of primary afferent neurons and nerve endings. Changes occurring in the gastrointestinal tract are transmitted to the brain via the vagal nerve. The gastrointestinal tract also harbors different cell groups that release cytokines and neuroendocrine hormones that play an important role in the body's response to infection and inflammation. Heijtz and Clarke, investigating the relationship between gut

microbiota and disorders associated with the central nervous system and neuropsychiatric diseases, suggested a bidirectional interaction between the brain and the gut [11, 12]. Also, researchers have reported that this interaction is mediated through the neuroendocrine, autonomic, and enteric nervous systems and the immune system. This dynamic pathway, called the 'Gut-Brain axis', involves many tissues and organs such as the brain, secretory glands, gut, immune cells, and gut microbiota [13] (Figure 1).

The pathways and mechanisms thought to be involved in the Gut-Brain axis.

2.1.Vagal Nerve (N. Vagus): The 10th cranial nerve, N. Vagus, carries afferent and efferent nerve fibers related to motor, sensory and autonomic nervous systems [14]. It has important functions related to respiratory, circulatory, and digestive functions and forms a direct connection between the gut and the brain [14]. In the literature, it has been reported that c-FOS levels were increased in vagal sensory ganglia and some brain regions of animals infected with pathogenic *Citrobacter rodentium* and *Campylobacter jejuni* and that this bacterial alteration in the gastrointestinal tract may be associated with anxiety symptoms [15, 16].

2.2. Cell Wall Components and Immune Responses: The gut microbiota has a peptidoglycan cell wall structure that activates both humoral and cellular immunity. The cell wall of gram-negative bacteria in the microbiota contains peptidoglycan monomers, lipopolysaccharides (LPS), porins, and mannose-enriched glycans, while the cell wall of gram-positive bacteria contains peptidoglycan monomers and lipoteichoic acids [17]. These components in the cell wall structure can stimulate intestinal epithelial cells and trigger the production of molecules associated with neural signaling pathways. The humoral immune response is activated by the binding of pro-inflammatory microbial components known as pathogen-associated molecular patterns (PAMPs) to pattern recognition receptors (PRPs) such as Toll-like receptors (TLRs) and NOD-like receptors (NODs) on intestinal epithelial cell surfaces. This activation triggers the release of inflammatory cytokines and acts directly on the brain where the permeability of the blood-brain barrier permits and indirectly through the vagal nerve where it does not [7]. In addition, these microbial components support the development of the immune system by antigen presentation to immune cells such as lymphocytes and macrophages [18]. The lipopolysaccharide (LPS) structure in the cell wall

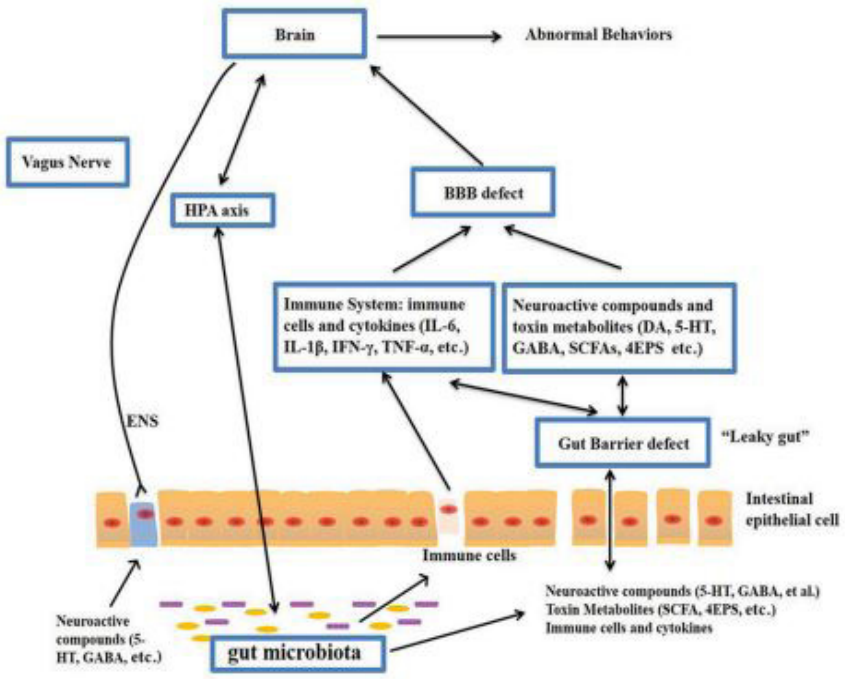


Figure 1: *The relationship between the gut microbiota and ASD[13]*

of gram-negative bacteria increases intestinal alkaline phosphatase production together with immunoglobulin A (Ig A), while the peptidoglycan layer enables the maturation of lymph follicles through NLR (NOD-like receptor). Maturing lymph follicles recognize intestinal bacterial flora via TLR (Toll-like receptor) and help cluster B lymphocytes [7, 18]. Further studies are needed to clarify the relationship between gut microbiota and the immune system.

2.3. Metabolites of the Gut Microbiota: Metabolites and nutritional components produced by microbial fermentation have important effects on brain function and immune response. One of the most important functions of the gut microbiota is the digestion of undigested nutrients through fermentation and the production of short-chain fatty acids (SCFA), which are an important source of energy for intestinal epithelial cells [7]. Short-chain fatty acids, including products such as acetate, propionate, butyrate, and lactate, support the immune system by preventing the accumulation of toxic substances as well as being an energy source for the body [19]. In addition, gut microbiota helps regulate the metabolism of tryptophan, an essential amino acid.

• **Short-chain Fatty Acids (SCFA):** Fatty acids have many functions, such as being a source of energy for cells, being present in the membrane structure, being involved in cellular functions, regulating gene expression and signaling pathways, and being involved in the synthesis of other lipid-structured mediators such as eicosanoids, which are chemical messengers [19]. The brain is an organ rich in fatty acids and fatty acid derivatives such as eicosanoids, lecithin, glycerophospholipids, sphingolipids, and prostaglandins. While fatty acids trigger inflammation by binding to specific immune cells such as T lymphocytes, B lymphocytes, and macrophages, some short-chain fatty acids produced by microbial fermentation have anti-inflammatory effects [20]. Most of the short-chain fatty acids such as acetate, butyrate, isobutyrate, hexonate, and propionate are produced by *Eubacterium, Roseburia, Faecalibacterium, Bifidobacterium, Lactobacillus* and *Enterobacter* species in the gut microbiota [21]. In the literature, it has been reported that fatty acids affect intestinal permeability, alter the lipoprotein profile, increase immune system functions, and acidify colonic pH [22]. It has also been reported that short-chain fatty acids, which are also involved in the enteroendocrine signaling pathway, bind to G protein-coupled receptors (GPR43, GPR41) receptors and initiate the release of neuropeptides such as peptide YY, glucagon-like peptide (GLP-1) and help regulate body homeostasis [22].

• **Tryptophan:** Tryptophan, an essential amino acid, is the precursor of substances such as serotonin, melatonin, and niacin. Tryptophan follows one of three different metabolic pathways: incorporation into tissue proteins, oxidation (kynurenine), and hydroxylation (serotonin pathway). While 3-10% of tryptophan participates in the hydroxylation pathway that forms chemical messengers such as serotonin and melatonin, 90% or more of tryptophan participates in the oxidation pathway that breaks the indole ring in its structure and forms kynurenine, nicotinic acid, nicotinamide adenine dinucleotide (NAD) [23]. Some of the enzymes involved in this pathway, also called the 'kynurenine shunt', which is dominant in tryptophan metabolism, are produced by aerobic bacteria in the gut microbiota [24]. Dysregulation of this pathway has been associated with many disorders in the central nervous system and gastrointestinal system. Serotonin, known to be effective in the etiology of many psychiatric disorders such as depression, anxiety, and obsessive-compulsive disorder, is mostly found in the gastrointestinal tract and synthesized by enterochromaffin cells [25]. Low levels of tryptophan in plasma affect immune system functions. This interaction may play a role in central nervous system functions and the development of mood disorders. In studies conducted to elaborate the anti-depressant properties of probiotics, it was observed that rats fed probiotics containing *Bifidobacterium infantis (B.infantis)* had decreased levels of pro-inflammatory cytokines, increased plasma tryptophan levels and decreased depressive behaviors of these rats [26]. It was also found that probiotic treatment caused a decrease in serotonin and dopamine destruction in the frontal cortex and amygdala [26].

2.4 Neurotransmitters and Neuropeptides: Neurotransmitters are chemical messengers responsible for signal transmission between neurons. Neuropeptides, which have different structures and properties than neurotransmitters, interact with different receptors in the brain and provide communication between neurons. These protein substances are responsible for specific

behavioral patterns [27]. Studies to date have shown that bacterial species in the gut microbiota such as *Lactobacillus, Bifidobacterium, Escherichia, Enterococcus,* and *Truchuris* produce neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin and some neuropeptides such as brain-derived neurotrophic factor (BDNF) [28]. These substances are associated with neuronal signal transduction and are thought to be involved in the regulation of brain function and behavior [28].

• **Gamma-Aminobutyric Acid (GABA):** GABA is an inhibitory neurotransmitter in the mature brain and an excitatory neurotransmitter in the developing brain [29]. Synthesized from glutamate, an excitatory amino acid, GABA acts as a second messenger in important body functions such as cellular development, homeostasis, and autophagy. The imbalance between GABA and excitatory and inhibitory neurotransmitters in the central nervous system is thought to be effective in the etiopathogenesis of various neuropsychiatric disorders such as memory loss, autism, epilepsy, anxiety, and depression [29]. Barett et al. realized that some bacterial species, such as *Lactobacillus* and *Bifidobacterium* synthesize GABA from glutamate in culture media [30]. Bravo et al. showed that *L. rhamnosus* regulates the production of central GABA receptors in some parts of the brain in animal models and suggested that this bacterial species may be useful in the treatment of depression and anxiety [31].

•**Serotonin:** Serotonin, a monoamine neurotransmitter, is involved in the regulation of many physiological processes in the central nervous system, such as mood, sleep, pain, aggression, sexual behavior, memory, and learning functions [32]. Serotonin in the gastrointestinal tract is responsible for the regulation of blood flow, motility, and secretory functions together with other intestinal hormones. It is known that serotonin, mostly synthesized by enterochromaffin cells in the gastrointestinal tract, is also synthesized by bacteria such as *Escherichia* and *Enterococcus* in the gut microbiota and that gut microbiota metabolites (short-chain fatty acids) trigger this synthesis [33].

• **Brain-derived neurotrophic Factor (BDNF):** BDNF is a neuroprotective peptide produced in the central nervous system. This structure, which can cross the blood-brain barrier, is responsible for the development and differentiation of neurons in childhood and ensures that neurons live a healthy life in adulthood [34]. In recent studies, plasma BDNF levels were found to be low in neurodegenerative diseases such as Alzheimer's, and Parkinson's and some psychiatric diseases such as depression and it was thought that BDNF synthesizing mRNA and protein levels are related to gut microbiota [35]. In experimental studies, increased hippocampal BDNF levels were found in mice free of specific pathogens [34]. It was observed that hippocampal BDNF m-RNA levels decreased in mice after infection with *Truchuris muris*, whereas BDNF levels increased to normal values after infection with *B.longum* [36]. On the other hand, Esworthy observed behavioral changes with increasing BDNF levels in male mice free of specific pathogens [37]. Given the role of BDNF in neuroplasticity and neuropsychiatric disorders, there is a need to elaborate on the relationship between BDNF and gut microbiota and to determine the conditions that affect this interaction.

3. The Relationship Between Gut Microbiota and Disease:

The gut microbiota is thought to play a role in the etiology of metabolic diseases such as obesity, diabetes, autoimmune diseases, neurodegenerative diseases, and psychiatric diseases such as autism spectrum disorder, depression, anxiety disorder, etc. Changes in the number, structure, and content of the gut microbiota cause the balance to be disrupted and 'unhealthy microbiota', also known as 'dysbiosis', to occur. This may result in local and systemic effects such as altered production of short-chain fatty acids, increased intestinal permeability, and decreased colonic resistance [8].

As a result of increased intestinal permeability, it is suggested that bacterial products pass into the systemic and local circulation, and as a result, they cause metabolic diseases such as obesity, metabolic syndrome, atherosclerosis, and diabetes by creating a low level of endotoxemia, or by affecting lipid and glucose metabolism or causing inflammation due to the change in short-chain fatty acid production [38]. Molecular similarity can be observed between products of the gut microbiota and cellular structures. It has been reported that dysbiosis may cause the production of some autoantibodies against these bacterial structures and may cause autoimmune diseases by negatively affecting healthy cells due to similarity [37]. However, decreased colon resistance is also said to predispose to infections with opportunistic pathogens or pathogenic bacteria.

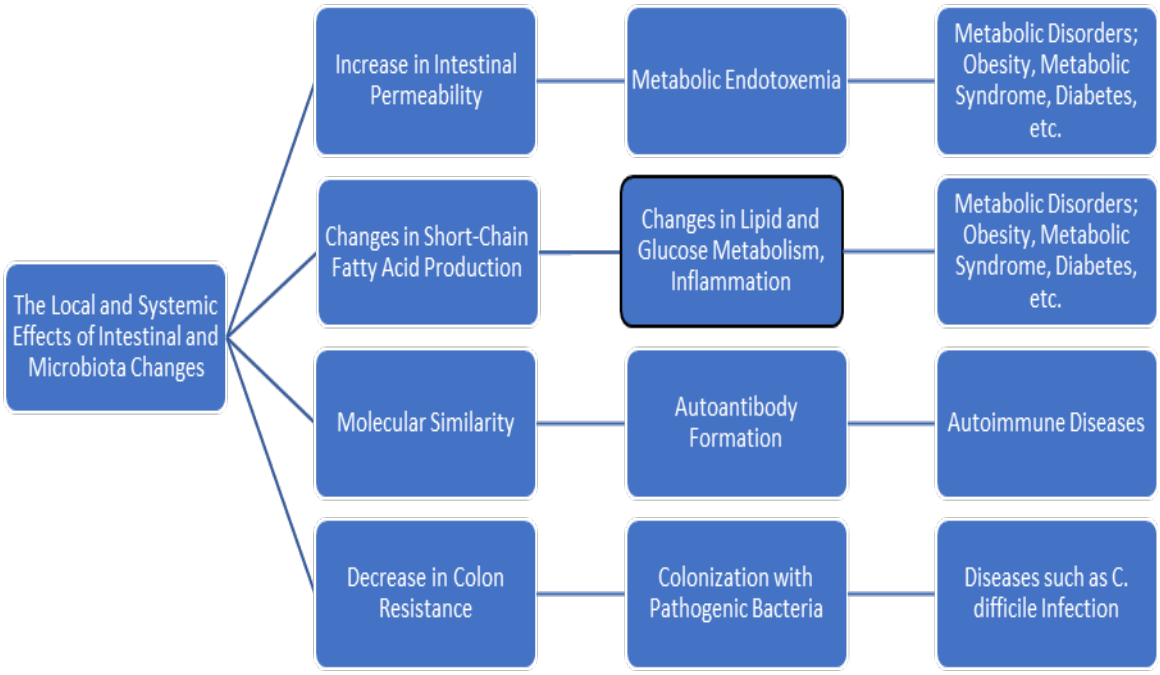


Figure 2. *Local and systemic effects of gut microbiota alteration* [40]

The positive neurochemical and physiological effects of chemical substances produced by healthy microbiota by binding to receptors on the intestinal surface or in different cells are thought to be negatively affected by dysbiosis [38]. Abnormal gut microbiota is thought to cause disruptions in the functioning of sulfur metabolism, increased oxidative stress, mitochondrial dysfunction, and neuroinflammation [39]. These changes may affect the structure and functioning of other systems, especially the central nervous system, and may cause diseases [39] (Figure 2).

4. The Gut-Brain Axis and Autism Spectrum Disorder (ASD)

The relationship between the gut microbiota and autism spectrum disorder, whose etiopathogenesis has not yet been fully explained and lacks a curative treatment, has been under investigation in recent years.In the literature, it has been shown that the majority of individuals with ASD are accompanied by gastrointestinal symptoms such as constipation, diarrhea, bloating, and indigestion and that these symptoms are associated with the degree of deficits in social relationships and social interactions and the severity of stereotypic behaviors, hyperactivity, and aggression in individuals with ASD [3, 4]. Furthermore, researchers have also reported that the gut microbiota content and distribution of individuals with autism differ from healthy children [4, 41].

Three main mechanisms have been proposed for the relationship between ASD and the gut-brain axis. The first is bacterial overload and/or abnormal bacterial diversity; the second is oxidative stress and disturbances in sulfur metabolism; and the third is increased intestinal wall permeability, called as “leaky gut hypothesis” [39].

4.1 Abnormal Intestinal Contents and/or Bacterial Overload

In the gastrointestinal tract, microorganisms are most abundant in the colon and these bacteria constitute the majority of microorganisms [42]. Bacterial colonization begins at birth. The intestinal flora of babies born vaginally is compatible with the vaginal flora of the mother and is predominantly *Lactobacillus*, while those born by cesarean section are predominantly *Clostridium*. In the first year, the flora is dominated by *Actinobacteria* and *Proteobacteria*, whereas around 2 years of age, the flora becomes similar to adult flora and *Firmicutes, Bacteroidetes,* and *Actinobacteria*, especially *Bifidobacterium*, predominate [43]. The majority of the intestinal microbial community is composed of five phyla: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria,* and *Verrucomicrobia*. The main members of the *Firmicutes* include the genera *Clostridium, Lactobacillus,* and *Ruminococcus*. *Firmicutes* and *Bacteroidetes* account for more than 90% of the known

phylogenetic categories [44]. Furthermore, the gut microbiota contains a balance of bacteria such as *Bifidobacterium* and *Lactobacillus* that produce anti-inflammatory cytokines and bacteria such as *Clostridium* and *Ruminococcus* that produce pro-inflammatory cytokines [39]. When the classes of bacteria colonized in the intestines were examined, the *Bacteroidetes* family was found at a higher rate in children with autism, while the *Firmicutes* family was found to be dominant in the control group [45]. Tomova et al. showed a significant decrease in *Bacteroidetes/Firmicutes* ratios and an increase in the amount of *Lactobacillus spp*. These results were consistent with the results of a study by Adams et al. showing that *Lactobacillus spp.* strains were significantly higher in individuals with autism [46]. In addition, an increase in *Clostridium spp*. strains was also found in a group of studies conducted at different times [47]. In different studies, *Actinobacter* and *Proteobacterium* branches differed in children with autism, and fewer *Bifidobacter spp*. were detected in individuals with autism [48]. In addition, *Desulfovibrio spp*. was found to be significantly overabundant [45]. Another remarkable result in the study by Tomova et al. was that the *Bacteroidetes/Firmicutes* ratio and the amounts of *Desulfovibrio spp.* and *Bifidobacterium spp*. were restored and returned to normal after giving probiotics containing *Lactobacillus, Bifidobacterium* and *Streptococcus* strains to children with ASD [49]. In a study conducted with children with autism who had gastrointestinal complaints, a high amount of *Sutterella spp*. was found in biopsy samples taken from individuals [50], while *Parasutterella excrementihominis*, a member of this family, was found in high amounts in stool samples [51]. In a 2000 clinical study by Sandler and Finegold, 8 out of 10 patients with late-onset autism who were treated with vancomycin for a short period showed transient improvement [52]. The researcher attributed this effect to the elimination of neurotoxin produced by the pathogens and stated that this improvement was transient as spores and toxins continued to multiply after vancomycin treatment was discontinued [52]. In a study conducted in Turkey in which ASD patients and their siblings were included, it was found that the total bacterial load decreased in both the ASD group and their siblings. In addition, in the same study, no statistically significant difference was found between *Bacteroidetes, Lactobacillus, Clostridium, and Desulfovibrio* species, but a difference was found between *Firmicutes* and *Bifidobacterium* species [53].

4.2 Oxidative Stress and Disorders of Sulfur Metabolism

Cysteine, which is a rate limiter in the synthesis of glutathione, the body's natural antioxidant, is synthesized from methionine, and disruption in this pathway leads to a decrease in cysteine and glutathione synthesis. It is thought that a deficiency in methionine synthesis may cause diseases such as autism by inhibiting gene expression [39]. Studies on gut microbiota and genetics suggest that genetic makeup may affect bacterial content. Furthermore, twins living in separate regions were found to have mostly similar bacterial content even years later [54]. These results showed that methionine deficiencies may cause alterations in the gut microbiota content in individuals with ASD [39]. In a different study in the literature, it was found that the amount of glutathione was lower and the ratio of oxidized glutathione to reduced glutathione was higher in individuals with ASD and this was associated with oxidative stress [55]. Recurrent infections, neuroinflammation, gastrointestinal inflammation, and metabolic disorders have been found more frequently in children with autism due to the important role of glutathione in the detoxification of heavy metals and toxic substances [55]. Disruptions in the transsulfuration mechanism along with increased oxidative stress have caused individuals with ASD to become more susceptible to the toxic effects of heavy metals, especially phenol-containing xenobiotics [56].

Desulfovibrio is a type of bacteria that reduces sulfate by consuming hydrogen gas in some chemical reactions. Another group of microorganisms that consume hydrogen in the absence of oxygen to form non-toxic methane are metagenic archaea [57]. Humans usually have one of two groups. If a sulfate-reducing bacterial group is present, it competes with archaea for hydrogen consumption and thermodynamically manipulates reactions in its favor. As a result, sulfate-reducing bacteria use hydrogen to form hydrogen sulfide, which is harmful to the human body [39]. *Desulfovibiro,* which differs from other bacteria in its ability to catabolize sulfur-containing compounds, can synthesize methionine and/or cysteine using sulfate as an electron acceptor [57]. It is thought that the deficiencies in sulfur metabolism seen in individuals with ASD may have

increased their need for *Desulfovibiro spp.* bacteria and that SAH, which increases due to disruptions in this pathway, may have increased by using *Desulfovibiro* to support growth and development [39].

4.3 Increased Intestinal Wall Permeability (the 'Leaky Gut' Hypothesis)

The term 'leaky gut' refers to the impaired barrier function that forms the wall of the small and large intestines [8]. It is thought that local endotoxemia and inflammation caused by disruption of this barrier, which is composed of tight junctions, epithelial cells, and various protein structures in the paracellular space, pass into the systemic circulation, reach the blood-brain barrier, and cause neuroinflammation, leading to neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder (ADHD) [42]. Toxins produced by *Clostridia* and *Desulfovibrio* bacteria, lipopolysaccharides (LPS) found in the cell walls of gram-negative bacteria such as *Bacteroides*, heavy metals, and phenol-containing compounds that cannot be excreted from the body due to inadequate antioxidant and detoxification mechanisms are suggested to cause inflammation and impair intestinal wall permeability [58]. It is thought that the decreased amount of *Bifidobacteria,* despite the increased amount of *Clostridia* detected in the stool analysis of individuals with autism, shifts the balance between inflammatory cytokines in favor of pro-inflammatory cytokines, triggers an inflammatory response in the intestines, and the epithelial barrier exposed to this response for a long time is damaged and causes an increase in intestinal permeability [42]. At the same time, it has also been suggested in the literature that *Clostridium difficile* toxins cause rounding of intestinal epithelial cells through Rho-GTPase activity, increasing paracellular space, and impaired function of the intestinal epithelial barrier [59]. It is known that the lipopolysaccharide (LPS) structure, also known as endotoxin, found in the cell wall of Gram-negative bacteria can pass into the systemic circulation with impaired intestinal permeability. Serum endotoxin level is said to be an indicator of bacterial load passing from the intestines to the systemic circulation [53]. Long-term exposure to endotoxin, which can cross the blood-brain barrier, has been found to cause neuronal cell death and lead to chronic neuroinflammation. It is thought that the intestinal mucosal barrier with increased permeability in individuals with ASD allows the passage of high amounts of bacteria and metabolites; these structures reaching the central nervous system trigger immune reactions, initiate neuroinflammation, and cause autism [8]. In the study conducted by Yitik Tonkaz et al. investigating the leaky gut hypothesis, it was found that intestinal microbiota was similar between ASD and sibling groups; biological markers of bacterial translocation were significantly different in the sibling group, whereas fecal calprotectin levels indicating local inflammation did not differ between the groups. The authors stated that the findings of the study did not support the leaky gut hypothesis in the etiology of autism [53].

Conclusion

The central nervous system is a dynamic structure that develops through molecules and transmission pathways within itself and through interaction with external factors. The gut microbiota is one of the external factors affecting development. Although altered gut microbiota have been found in children with ASD, whether this is a cause or effect is still unknown. In studies investigating the relationship between ASD and gut microbiota, the heterogeneity of patients in terms of factors such as age range, diet, and probiotic use prevents generalization of the results. It should also be noted that most of the studies were cross-sectional and mainly investigated bacteria. The bidirectional nature of the microbiota-gut-brain axis makes it difficult to determine the first place where the problem started and to establish a cause-and-effect relationship. Double-blind, placebo-controlled, prospective studies with a homogeneous distribution of participants are needed.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Ethical Declaration:

The study was conducted in accordance with the criteria of the Declaration of Helsinki.

Authors' Contributions: Concept: G.Y.T., B.S.O., Design: G.Y.T., B.S.O., Data Collection or Processing: G.Y.T., B.S.O., E.C., Analysis or Interpretation: G.Y.T., B.S.O., Literature Search: G.Y.T., B.S.O., E.C., Writing: G.Y.T., B.S.O., E.C.

References

1. Association AP. American Psychiatric Association DSM-5 Task Force.(2013). Diagnostic and statistical manual of mental disorders: DSM.5.

2. Maenner MJ, Warren Z, Williams AR, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. *MMWR Surveill Summ.* 2023;72(2):1-14.

3. Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Alhawamdeh R. Role of gastrointestinal health in managing children with autism spectrum disorder. *World J Clin Pediatr.* 2023;12(4):171-96.

4. Santocchi E, Guiducci L, Fulceri F, et al. Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. *BMC Psychiatry.* 2016;16:183. Published 2016 Jun 4.

5. Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. *Front Physiol.* 2011;2:94. Published 2011 Dec 7.

6. Sartor RB. Microbial influences in inflammatory bowel diseases. *Gastroenterology.* 2008;134(2):577-594.

7. Mangiola F, Ianiro G, Franceschi F, Fagiuoli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. *World J Gastroenterol.* 2016;22(1):361-368.

8. Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E. The Microbiota-Gut-Brain Axis in Psychiatric Disorders. *Int J Mol Sci.* 2022;23(19):11245. Published 2022 Sep 24.

9. Chen Y, Zhou J, Wang L. Role and Mechanism of Gut Microbiota in Human Disease. *Front Cell Infect Microbiol.* 2021;11:625913. Published 2021 Mar 17.

10. Rieder R, Wisniewski PJ, Alderman BL, Campbell SC. Microbes and mental health: A review. *Brain Behav Immun.* 2017;66:9-17.

11. Clarke G, Grenham S, Scully P, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry.* 2013;18(6):666-673.

12. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A.* 2011;108(7):3047-3052.

13. Li Q, Han Y, Dy ABC, Hagerman RJ. The Gut Microbiota and Autism Spectrum Disorders. *Front Cell Neurosci.* 2017;11:120. Published 2017 Apr 28.

14.Konsman JP, Luheshi GN, Bluthé RM, Dantzer R. The vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis. *Eur J Neurosci.* 2000;12(12):4434-4446.

15. Goehler LE, Park SM, Opitz N, Lyte M, Gaykema RP. Campylobacter jejuni infection increases anxiety-like behavior in the holeboard: possible anatomical substrates for viscerosensory modulation of exploratory behavior. *Brain Behav Immun.* 2008;22(3):354-366.

16. Lyte M, Li W, Opitz N, Gaykema RP, Goehler LE. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia Citrobacter rodentium. *Physiol Behav.* 2006;89(3):350-357.

17. Forsythe P, Kunze WA. Voices from within: gut microbes and the CNS. *Cell Mol Life Sci.* 2013;70(1):55-69.

18. Bouskra D, Brézillon C, Bérard M, et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature.* 2008;456(7221):507-510.

19. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. *Proc Nutr Soc.* 2003;62(1):67-72.

20. Holmes E, Kinross J, Gibson GR, et al. Therapeutic modulation of microbiota-host metabolic interactions. *Sci Transl Med.* 2012;4(137):137rv6.

21. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. *Science.* 2012;336(6086):1262-1267.

22. MacFabe DF. Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders.

Microb Ecol Health Dis. 2015;26:28177. Published 2015 May 29.

23. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. *Clin Chim Acta.* 2006;364(1-2):82-90.

24. Kurnasov O, Jablonski L, Polanuyer B, Dorrestein P, Begley T, Osterman A. Aerobic tryptophan degradation pathway in bacteria: novel kynurenine formamidase. *FEMS Microbiol Lett.* 2003;227(2):219-227.

25. Varma GS. Major Depresif Bozuklukta Nöroinflamatuvar Hipotez/Neuroinflammatory Hypothesis in Major Depressive Disorder. *Psikiyatride Guncel Yaklasimlar.* 2014;6(1):1.

26. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience.* 2010;170(4):1179-1188.

27. Fiş NP, Berkem M. Nörotransmitter Sistemlerinin Gelişimi ve Psikopatolojiye Yansımaları. *Klinik Psikofarmakoloji Bulteni*. 2009;19: 312-321

28. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine [published correction appears in J Appl Microbiol. 2014 May;116(5):1384-6]. *J Appl Microbiol.* 2012;113(2):411-417.

29. Smith-Hicks CL. GABAergic dysfunction in pediatric neuro-developmental disorders. *Front Cell Neurosci.* 2013;7:269. Published 2013 Dec 19.

30. Barrett E, Ross R, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. *J Appl Microbiol.* 2012;113(2):411-417.

31. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A.* 2011;108(38):16050-16055.

32. Lam KS, Aman MG, Arnold LE. Neurochemical correlates of autistic disorder: a review of the literature. *Res Dev Disabil.* 2006;27(3):254-289.

33. Reigstad CS, Salmonson CE, Rainey JF 3rd, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J.* 2015;29(4):1395-1403.

34. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology.* 2011;141(2):599-609.e6093.

35. Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Res Brain Res Rev.* 2004;45(2):104-114.

36. Bercik P, Verdu EF, Foster JA, et al. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology.* 2010;139(6):2102-2112.e1.

37. Esworthy RS, Smith DD, Chu FF. A Strong Impact of Genetic Background on Gut Microflora in Mice. *Int J Inflam.* 2010;2010(2010):986046. doi:10.4061/2010/986046

38. Zhu J, Guo M, Yang T, et al. *Zhonghua Er Ke Za Zhi.* 2017;55(12):905-910.

39. Heberling CA, Dhurjati PS, Sasser M. Hypothesis for a systems connectivity model of Autism Spectrum Disorder pathogenesis: links to gut bacteria, oxidative stress, and intestinal permeability. *Med Hypotheses.* 2013;80(3):264-270.

40. Yalçın SS, KanatlıMÇ. İntestinal mikrobiyota transplantasyonu; neden, kime, nasıl? *Pamukkale Medical Journal.* 2015(2):148-54.

41. Mayer EA, Padua D, Tillisch K. Altered brain-gut axis in autism: comorbidity or causative mechanisms?. *Bioessays.* 2014;36(10):933-939.

42. Fattorusso A, Di Genova L, Dell'Isola GB, Mencaroni E, Esposito S. Autism Spectrum Disorders and the Gut Microbiota. *Nutrients.* 2019;11(3):521. Published 2019 Feb 28.

43. Socała K, Doboszewska U, Szopa A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacol Res.* 2021;172:105840.

44. Ersöz Alan B, Gülerman F. Otizm Spektrum Bozukluğunda Bağırsak Mikrobiyotasının Rolü [The Role of Gut Microbiota in Autism Spectrum Disorder]. *Turk Psikiyatri Derg.* 2019;30(3):210-219.

45. Finegold SM, Dowd SE, Gontcharova V, et al. Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe.* 2010;16(4):444-453.

46. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol.* 2011;11:22. Published 2011 Mar 16.

47. Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med Microbiol.* 2005;54(Pt 10):987-991.

48. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol.* 2011;11:22. Published 2011 Mar 16.

49. Tomova A, Husarova V, Lakatosova S, et al. Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav.* 2015;138:179-187.

50. Williams BL, Hornig M, Parekh T, Lipkin WI. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *mBio.* 2012;3(1):e00261-11. Published 2012 Jan 10.

51. De Angelis M, Piccolo M, Vannini L, et al. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. *PLoS One.* 2013;8(10):e76993. Published 2013 Oct 9.

52. Sandler RH, Finegold SM, Bolte ER, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol.* 2000;15(7):429-435.

53. Yitik Tonkaz G, Esin IS, Turan B, Uslu H, Dursun OB. Determinants of Leaky Gut and Gut Microbiota Differences in Children With Autism Spectrum Disorder and Their Siblings. *J Autism Dev Disord.* 2023;53(7):2703-2716.

54. Dicksved J, Halfvarson J, Rosenquist M, et al. Molecular analysis of the gut microbiota of identical twins with Crohn's disease. *ISME J.* 2008;2(7):716-727.

55. Geier DA, Geier MR. A clinical and laboratory evaluation of methionine cycle-transsulfuration and androgen pathway markers in children with autistic disorders. *Horm Res.* 2006;66(4):182-188.

56. Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Geier MR. A prospective study of transsulfuration biomarkers in autistic disorders [published correction appears in Neurochem Res. 2009 Feb;34(2):394]. *Neurochem Res.* 2009;34(2):386-393.

57. Nirmalkar K, Qureshi F, Kang DW, Hahn J, Adams JB, Krajmalnik-Brown R. Shotgun Metagenomics Study Suggests Alteration in Sulfur Metabolism and Oxidative Stress in Children with Autism and Improvement after Microbiota Transfer Therapy. *Int J Mol Sci.* 2022;23(21):13481. Published 2022 Nov 3.

58. Xu M, Xu X, Li J, Li F. Association Between Gut Microbiota and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Front Psychiatry.* 2019;10:473. Published 2019 Jul 17.

59. Aktories K, Just I. Clostridial Rho-inhibiting protein toxins. *Curr Top Microbiol Immunol.* 2005;291:113-145.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Investigation of widespread pain and other musculoskeletal symptoms among athletes registered to Havza Youth and Sports District Directorate

Tuba MIZRAK[1]
İlker İLHANLI[2]
Manolya İLHANLI[3]
Mustafa ŞAHİN[4]
Zennure ORUN YALÇIN[4]

1. *Ondokuz Mayıs University Havza Physical Therapy and Rehabilitation Center, Samsun, Turkey*
2. *Ondokuz Mayıs University Faculty of Medicine Department of Physical Medicine and Rehabilitation, Samsun, Turkey*
3. *Ondokuz Mayıs University Faculty of Dentistry Multidisciplinary clinics, Samsun, Turkey*
4. *Turkish Republic Ministry of Health Havza District Health Directorate, Samsun, Turkey*

Received: 26 December 2023
Accepted: 16 January 2024
Published: 31 January 2024

Corresponding Author: Manolya İLHANLI Dt. PhD., Ondokuz Mayıs University Faculty of Dentistry Multidisciplinary clinics, 55139, Samsun, Turkey.

E-mail: manolya_dmrcn@hotmail.com

Abstract

Objective

Youth centers are institutions that bring children from different age groups together and encourage sports. The prevalence of widespread pain is high in school-age children. It was aimed to examine widespread pain and other musculoskeletal symptoms in athletes registered with Havza Youth and Sports District Directorate and attending the Youth Center, and to evaluate their effects on school success and absenteeism. Aim of the study was expanded to evaluate short-term changes in terms of musculoskeletal problems after provided exercise training.

Methods

Participants' school success, absence periods in the last month, pain complaints, duration and intensity, presence of tender points, frequency of complaints other than pain, temporomandibular joint complaints, depression (Depression Scale developed for children) and quality of life (PEDsQL 4.0) scores were examined.

Results

29 athletes (12.1±1.4 years old) were included in the study. 11 athletes participated in the evaluation one month after the training. After the training, the frequency of complaints other than pain and the frequency of tender points were numerically lower. While there were 2 athletes who reported having chronic (>3 months) pain before training, there were no athletes who had chronic pain after training. The number of athletes with non-chronic pain decreased from 10 to 6. There was no significant difference between those with chronic pain, those with non-chronic pain, and those without pain in terms of self-evaluation of school success and success grade ($p=0.694$ and $p=0.094$, respectively). Discontinuation was significantly less in those without pain ($p=0.008$). No significant difference was detected between before and after training for depression and quality of life scores ($p>0.05$).

Conclusion

Widespread chronic pain is not common in athlete children, but non-chronic pain is more common. Training and exercise programs to cope with musculoskeletal problems may reduce the frequency of pain in the short term.

Keywords: Musculoskeletal system, Sports, Widespread pain

You may cite this article as: Mızrak T, İlhanlı İ, İlhanli M, Şahin M, Orun Yalçın Z. Investigation of widespread pain and other musculoskeletal symptoms among athletes registered to Havza Youth and Sports District Directorate. *Cerasus J Med*. 2024;1(1):12-19.

Introduction

Sports are physical activities that people do within systematic and regular rules in order to win and be successful by using their determination to fight. It is clear that sports have positive effects on adults who will assume responsibility in society to acquire good habits and establish healthy relationships with individuals and society. For this reason, great importance is given to sports in developed countries and children are encouraged to participate in sports and physical education programs starting from an early age [1,2]. It is a conscious effort that maintains the strength and agility of the body and increases willpower, as well as the desire to break records, excel and win. Sports is a competition-based activity that is embodied in various branches by specializing physical education activities and requires physiological, psychological and aesthetic technical features when performed at a high level and is surrounded by a number of rules [3]. It is expected that the physical and mental health of children who do sports will be positively affected. Youth centers provide artistic, social, cultural, educational and sports activities, historical and cultural events in order to help young people spend their free time in a positive way, to contribute to the development of young people, to provide guidance and consultancy to young people, as well as to raise awareness of young people against harmful habits and keep them away from them. These are centers that organize trips and camps [4]. In this context, youth centers have an important place as institutions that bring together children from different age groups and encourage them to do sports, thus aiming to protect and improve the physical and mental health of children and young people. Considering this situation, the frequency of widespread chronic pain may be expected to be less in children attending youth centers, while the frequency of sports-related acute pain may be expected to be higher. Chronic widespread musculoskeletal pain is a common musculoskeletal disorder affecting 15% of the general population [5]. The prevalence of widespread pain is high in school-age children [6]. A part of musculoskeletal system, temporomandibular joint (TMJ) pain may be frequently seen in childhood and adolescents [7]. This can be due to parafunctional habits, bruxism and nail biting and may be aggravated by the emotional stress [7]. Depression may be associated with musculoskeletal pain. According to the definition of the World Health Organization (WHO), depression; It is a condition characterized by the inability to perform daily activities, a constant state of sadness, and loss of interest for at least two weeks [8]. Depression is associated with poor school performance and absenteeism. Since it is a common problem of childhood, early diagnosis and diagnosis of the disorder, appropriate psychological help and more comprehensive and successful treatment approaches can prevent more complex and serious problems in adulthood [6].

This study aimed to examine widespread pain and other musculoskeletal symptoms in athletes registered with Havza Youth and Sports District Directorate and attending the Youth Center, and to evaluate their effects on school success and absenteeism. In addition, the aim of the study was expanded to evaluate short-term changes in terms of musculoskeletal problems before and after training by providing exercise training and coping with musculoskeletal system problems.

Methods

After the necessary permissions for the project were obtained from the relevant institutions, a protocol was signed between the institutions and organizations supporting the project. Within the scope of the project, whose ethical compliance was approved by the Youth and Sports Directorate, a sample of 29 athletes, 22 boys and 7 girls, who were registered to the Havza Youth and Sports District Directorate and attending the Youth Center, who volunteered to participate in the study, were determined. The study was conducted in accordance with the principles of the Declaration of Helsinki and written consents of all participants were obtained. All participants were questioned and examined using structured questionnaires by the researchers. Musculoskeletal examination of the participants including posture, motor function, sensation, deep tendon reflexes, tender points and trigger points were done by the same physician and the abnormalities were recorded. TMJ examination were done by the dentists. Oral findings of bruxism, clicking and popping sounds, joint limitation, TMJ pain and masticatory muscle tenderness were examined and the findings were recorded. Training and exercises (posture, breathing, relaxation and strengthening) were given to cope with musculoskeletal system problems. Demographic information and examination findings of all participants were recorded. In addition to the demographic data of the participants, their school success (declared by the school administration), duration of absences in the last month (declared by the school administration), pain complaints, duration and severity (with visual pain scale: VAS), presence of tender points, complaints other than pain. Prevalence, depression (Depression Scale developed for children) and quality of life (PEDsQL 4.0) scores were examined. Volunteer students (N=11) were included in the re-evaluation one month after the training. The

data obtained was analyzed using descriptive statistics. Data that fit the normal distribution were given as mean± standard deviation, and data that did not fit were given as median (minimum-maximum). While the Chi-square test was used to compare frequencies between groups, T test or Mann-Whitney U test and Kruskal Wallis test were used to compare continuous variables between groups, depending on whether they fit into a normal distribution. Significance level was set $p<0.05$. SPSS 22 (IBM, USA) was used for statistical analysis.

Results

29 athletes were included in the study. 22 of the students were male (75.9%) and 7 were female (24.1%). The average age was 12.1±1.4 years. While the students' average height was 151.7±11.2 cm, their average weight was 43.7±11.6 kg and their average body mass index was 18.7±2.6 kg/m2. Some demographic data about the students' families are given in Table 1.

Table 1. Some demographic data of the participants regarding their families (N=29).

N= number of participants who answered the question		N (%)
Number of children in the family	1	3 (10.3)
	2	9 (31)
	3	14 (48.3)
	4	3 (10.3)
Birth order of the participant	1	9 (31)
	2	14 (48.3)
	3	6 (20.7)
Living in the same house with their family		27 (93.1)
Parents	Living together	28 (96.6)
	Divorced	1 (3.4)
Those with health insurance		27 (93.1)
Mothers' education	Literate	2 (6.9)
	Primary school	5 (17.2)
	Middle school	7 (24.1)
	High school	8 (27.6)
	College	7 (24.1)
Mothers' occupation	Housewife	22 (75.9)
	White collar employee	6 (20.7)
	Blue collar	1 (3.4)
Fathers' education	Literate	1 (3.4)
	Primary school	1 (3.4)
	Middle school	8 (27.6)
	High school	11 (37.9)
	College	8 (27.6)
Fathers' occupation	White collar employee	11 (37.9)
	Blue collar	6 (20.7)
	Farmer, tradesman	12(41.4)

29 people answered the question of the number of households. The average value of the number of households was 4.8±1.2.

While the average age of the mother was 39.5±5.6 years, the average age of the father was 42.5±6.3 years.

Students were asked to self-evaluate their school success before and one month after the training. Post-training self-assessment results were numerically better (Table 2).

The average success score of the participants was 85.9±11 points (N=20). The duration of school absence in the last month was 0 (0-10) days. The duration of absenteeism after the training was 2.5 (0-7) days (N=10), similar to before the training. Since no success grade was given in the last month, a score that could objectively evaluate success could not be obtained.

Most of the students had a group of friends. To the question "Do you have a group of friends?", 28 (96.6%) students answered yes and 1 (3.4%) student answered no. To the question "Do you have a group of friends after the training?", 10 (90.9%) students answered yes and 1 (9.1%) student answered no. There were no health complaints before the training (N=29). One of the participants (9.1%) had a complaint after the training (N = 11). None of the students had a rheumatological disease and no one was taking medication.

Table 2. Students' self-evaluation of their own school success.

	Before training (N=29)	After training (N=11)
Good	16 (55.2)	7 (63.6)
Average	11 (37.9)	3 (27.3)
Bad	2 (6.9)	1 (9.1)
N= The number of participants		

Table 3. Comparison of athletes with widespread chronic pain, non-chronic pain, and no pain.

	School success (number of participants)			
	Good	Average	Bad	P value
Widespread chronic pain	2	0	0	0.694
Non-chronic pain	2	2	0	
No pain	12	9	2	
	Success grade, median (minimum-maximum)			
Widespread chronic pain	98 (98-98)			0.094
Non-chronic pain	77 (77-77)			
No pain	85 (58-99)			
	Absence, day, median (minimum-maximum)			
Widespread chronic pain	2 (1-3)			0.008*
Non-chronic pain	10 (1-10)			
No pain	0 (0-5)			
* Significance level p<0.05				

At the first evaluation, 2 (6.9%) students had chronic pain complaints lasting more than 3 months. The number of people with pain for less than three months was 10 (34.5%). VAS median value was 2 (0-6). After the training, 6 (54.5%) students had pain complaints. None of them were among those who stated that they had pain for more than 3 months before the training. In other words, while 3 students whose pain was not chronic continued to have pain after the training, 3 students had complaints of pain that developed in the last month after the training. The median VAS value after training was 2 (2-6).

There was no difference in terms of self-evaluation of school success and success grades between those with widespread chronic pain, those with chronic pain, and those without pain (p=0.694 and p=0.094, respectively) (Table 3). In terms of absenteeism, absenteeism was significantly less in those without pain (p=0.008) (Table 3).

Complaints other than widespread pain were numerically less in the post-training evaluation. The frequency of complaints other than widespread pain in the first evaluation and in the evaluation made one month after the training is shown in Table 4.

Table 4. Frequency of complaints other than widespread pain.

	Before training (N=29)	After training (N=11)
	N (%)	N (%)
Chronic anxiety or tension	2 (6.9)	0
Exhaustion	12 (41.3)	5 (45.5)
Sleeping disorder	6 (20.7)	4 (36.4)
Chronic headache	1 (3.4)	0
İrritable bowel disease	0	0
Subjective soft tissue swelling	0	0
Numbness	6 (20.7)	1 (9.1)
Change in pain with physical activity	0	0
Change in pain due to weather conditions	2 (6.9)	1 (9.1)
Change in pain due to anxiety/stress	0	0
TMJ complaint/disorder	0	0
N= The number of participants		

Table 5. Frequency of tender points.

	Before training (N=29)	After training (N=11)
	N (%)	N (%)
Suboccipital	5 (17.2)	1 (9.1)
Trapezius	5 (17.2)	1 (9.1)
Supraspinatus	2 (6.9)	0
Gluteal	1 (3.4)	1 (9.1)
Trochanter major	1 (3.4)	2 (18.2)
Lower cervical	2 (6.9)	0
2. costa	1 (3.4)	0
Lateral epicondyle	3 (10.3)	1 (9.1)
Knee medial	5 (17.2)	3 (27.3)
N= The number of participants		

Table 6. Participants' depression and quality of life scores				
		Before training (N=29)	After training (N=11)	P value
Depression scale developed for children		23.3±5.7	24.8±3.7	0.177
PEDsQL 4.0	Physical function	67.9±15.3	69.9±13.4	0.725
	Emotional function	62.3±22.1	65±30	0.820
	Social function	80.5±22.6	82.7±18.8	0.654
	School function	60.9±19	63.6±28.8	0.790
	Psychological score	67.9±16.6	70.5±20.4	0.742
	Physical score	67.9±15.3	69.9±13.4	0.725
Significance level p<0.05, PEDsQL 4.0: pediatric quality of life inventory version 4.0				

The median time for morning stiffness before training was 6 (0-15) minutes (N=7). The median time for morning stiffness after training was 2 (1-30) minutes (N=6), similar to before training.

In the evaluation made one month later, the number of tender points detected by examination was numerically less (Table 5).

No significant difference was detected between the depression score, quality of life scores and all subgroups evaluated before and one month after the training (p>0.05) (Table 6).

Discussion

This study aimed to examine the widespread pain and other musculoskeletal symptoms of athlete children attending the youth center, to evaluate their impact on school success and absenteeism, and to also provide exercise training and coping with musculoskeletal system problems before and after the training. We aimed to evaluate the changes in the short term.

As a result of the study, in the evaluation one month after the training, the number of athletes with chronic pain, the number of athletes with non-chronic pain, the frequency of complaints other than pain, and the frequency of tender points were numerically lower.

In the study of Bilgiç and Duymaz [9], in which they investigated the effect of posture correcting exercises on pain, a decrease in pain scores was observed in the group in which posture exercises were applied, and in this respect, similar results were obtained with our study. It can be thought that low participation in the post-training evaluation affected the results. However, all students with chronic pain complaints participated in the second evaluation.

There was no difference between the groups in terms of self-evaluation of school success according to pain status. Many studies have found that participation in physical activity has positive effects on academic success. On the other hand, there are also studies indicating that participation in these activities has a negative effect on academic success [10]. Singh et al. [11] examined how physical activity affects students' school success, in the results obtained from long-term studies of 12,000 children and young people between the ages of 6-18, most of which were conducted in America. As a result of the research, students who were more physically active also had higher academic success [11].

Physical activity provides more blood and oxygen to the brain; It has been emphasized that it reduces stress and balances emotions by increasing endorphins, thus improving the person's cognitive system. Howe et al. [12] investigated how regular physical activity and sports participation affects academic performance on children aged 6-11. As a result of the research, they found that although an increase in academic performance was observed, the cognitive functions of children participating in physical activity also improved [12].

Although it is expected that those with widespread chronic pain will have worse school success, in our study there was no significant difference between the groups in terms of school success scores. This may not reflect real population data due to the small number of samples. However, as expected, absenteeism was significantly less in those without pain. In a study investigating depression and social support in 5530 university students from different countries, Steptoe et al. [13] found that the susceptibility to depression increased with lack of physical activity. In the same

study, the prevalence of depression symptoms in students in Eastern European countries was 43.2% and in students in Western European countries it was 23.5% [13]. There was no difference in depression and quality of life scores between the evaluations made before the training and one month after the training. This may be attributed to the short follow-up period or the fact that the athletes' psychological and physical scores are already good and it is easier to maintain this state of well-being.

Non -homogeneous small sample size restricted to a local area, short follow-up period and unsupervised exercise program are the main limitations of this study.

Conclusion

As a result, widespread chronic pain is not common in athlete children, but non-chronic pain is more common. In addition, the results we obtained with short-term exercise in this study showed that regular exercises will have a significant effect on pain and a minimal effect on depression score. Training and exercise programs to cope with musculoskeletal problems may reduce the frequency of pain in the short term. Studies with larger samples and longer follow-up are needed.

Acknowledgments: This study was prepared in the light of the results obtained within the scope of the project carried out with the contributions of Havza Municipality and Havza Local Action Group. Authors thanks to Havza District Health Directorate, Ondokuz Mayıs University Havza Physical Therapy and Rehabilitation Center, Havza Municipality, Havza Youth and Sports District Directorate and Havza Youth Center Directorate for their contributions.

Conflict of interest: Authors declared any conflict of interest.

Financial disclosure: This study was prepared in the light of the results obtained within the scope of the project carried out with the contributions of Havza Municipality and Havza Local Action Group. This project was supported by Havza Municipality financially with 1000 TL.

Concept: T.M., M.I., I.I., **Design:** T.M., M.I., I.I., **Data Collection or Processing:** T.M., M.I., I.I., M.S., Z.Y., **Analysis or Interpretation:** T.M., M.I., I.I., **Literature Search:** T.M., M.I., I.I., **Writing:** T.M., M.I., I.I.

References

1. Yücel M. Gelişim ve öğrenmenin spor kültürünün oluşmasına etkisi. *Fırat Üniversitesi Doğu Araştırmaları Dergisi (DAD)*. 2004;2(3):100-108.

2. Kotan Ç, Hergüner G, Yaman Ç. İlköğretim Okullarında Okuyan Sporcu öğrencilerin Spor Yapmalarında Okul Ve Aile Faktörünün Etkisi (Sakarya İl Örneği). *Niğde Üniversitesi Beden Eğitimi ve Spor Bilimleri Dergisi*. 2009; 3 (1): 49-58.

3. Kale R, Erşen E. Beden Eğitimi ve Spor Bilimlerine Giriş. İstanbul, Nobel Yayınevi; 2003.

4. Gençlik ve Spor Bakanlığı Gençlik Merkezleri Yönetmeliği, Madde 5, Resmi Gazete, sayı 31847. Available from: https://www.resmigazete.gov.tr/eskiler/2022/05/20220526-2.htm

5. Burri A, Lachance G, Williams FM. Prevalence and risk factors of sexual problems and sexual distress in a sample of women suffering from chronic widespread pain. *J Sex Med*. 2014;11(11):2772-2784.

6. Durmaz Y, Alayli G, Canbaz S, et al. Prevalence of juvenile fibromyalgia syndrome in an urban population of Turkish adolescents: impact on depressive symptoms, quality of life and school performance. *Chin Med J (Engl)*. 2013;126(19):3705-3711.

7. Minghelli B, Cardoso I, Porfírio M, et al. Prevalence of temporomandibular disorder in children and adolescents from public schools in southern portugal. *N Am J Med Sci*. 2014;6(3):126-132.

8. World Health Organization. Depression and other common mental diorders. 2019. Available from: https://iris.who.int/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?sequence=1

9. Bilgiç M, Duymaz T. Geç Ergenlik Döneminde Kısa Süreli Olarak Uygulanan Postür Düzeltici Egzersiz ve Germe Kombinasyonunun Esneklik, Ağrı ve Depresyon Puanı Üzerine Olan Etkisinin Araştırılması. *IGUSABDER*. 2018;4: 318-329.

10. Cheung CK, Kwok ST. Activities and Academic Achievement Among College Students. *The Journal of Genetic Psychology*. 2004;159(2): 147-162.

11. Singh A, Uijtdewilligen L, Twisk JW, van Mechelen W, Chinapaw MJ. Physical activity and performance at school: a systematic review of the literature including a methodological quality assessment. *Arch Pediatr Adolesc Med*. 2012;166(1):49-55.

12. Committee on Physical Activity and Physical Education in the School Environment; Food and Nutrition Board; Institute of Medicine; Kohl HW III, Cook HD, editors. Educating the Student Body: Taking Physical Activity and Physical Education to School. Washington (DC): National Academies Press (US); 2013 Oct 30. 4, Physical Activity, Fitness, and Physical Education: Effects on Academic Performance. Available from: https://www.ncbi.nlm.nih.gov/books/NBK201501/

13. Steptoe J, Wardle A. Depressive symptoms, social support, and personal health behaviors in young men and women. *Health Psychology*. 2001;20(3):223-227.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Maternofetal outcome and six months follow-up of pregnant patients with COVID-19 ARDS

Azime BULUT[1]
Fatma ALKAN BAYBURT[1]
Gizem AVCI[2]
Dilek YENİAY[3]
İlknur ŞENEL[4]
Gökhan ORDU[5]

1. *Asst. Prof., MD, Department of Anesthesiology and Reanimation, Giresun Training and Research Hospital,*
2. *MD, Department of Anesthesiology and Reanimation, Etlik City Hospital*
3. *MD, Department of Anesthesiology and Reanimation, Giresun Women's and Children's Health Education and Research Hospital*
4. *Asst. Prof.,MD, Department of Infectious Diseases and Clinical Microbiology, Giresun University*
5. *MD, Department of Obstetrics and Gynecology, Hayat Hospital*

Received: 21 December 2023
Accepted: 16 January 2024
Published: 31 January 2024

Corresponding Author: Azime BULUT, ORCID ID: 0000-0001-8164-5617

Department of Anesthesiology and Reanimation, Giresun University Faculty of Medicine, Giresun 28100, Turkey

E-mail: cimemazime@yahoo.com.tr

Abstract

Objective: In this study, it was aimed to evaluate pregnant patients followed in the intensive care unit (ICU) with severe acute respiratory distress syndrome due to COVID-19.

Material and methods: In this study, all pregnant patients infected with COVID-19 who were admitted to the ICU with the diagnosis of acute respiratory distress syndrome (ARDS) were evaluated retrospectively. Demographic, laboratory and clinical findings and follow-up of the mother and newborn at least 6 months after discharge were recorded.

Results: A total of 17 patients were included in this study. Three of the patients died in the ICU, 13 patients were discharged, 1 patient is still being followed up in the palliative care unit. 14 of 17 patients required mechanical ventilation and 11 patients were extubated. All patients had not been vaccinated. We detected tracheal stenosis in four of the eleven patients who were intubated and survived.

Conclusions: While managing pregnant patients with respiratory failure, making decisions about delivery timing remains the most controversial. Based on our experience, we can say that if the week of gestation is compatible with life, the decision to deliver should be taken before severe progression of the mother's respiratory distress. Tracheal stenosis formation caused by intubation should be suspected even in short intubation periods in pregnant patients. In this, the addition of factors such as giving prone position, not following appropriate cuff pressure to physiological changes in pregnancy is involved.

Keywords: Pregnancy, Covid-19, intensive care

You may cite this article as: Bulut A, Avcı G, Alkan Bayburt F, Yeniay D, Şenel İ, Ordu G. Maternofetal outcome and six months follow-up of pregnant patients with COVID-19 ARDS. *Cerasus J Med.* 2024;1(1):20-26.

Introduction

In late December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, China,with clinical presentations resembling those of viral pneumonia. Afterward, the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly leading to a global pandemic that cause clogging of the healthcare system [1]. All the countries were coping with the COVID-19 outbreak; hence, elective surgical procedures were postponed or cancelled except deliveries. We know that symptomatic pregnant patients who have tested positive for SARS-CoV-2 are at a higher risk of developing acute respiratory distress syndrome and adverse perinatal events(invasive ventilation, prematurity) than non-pregnant patients [2-7]. Underlying comorbidities, especially advanced maternal age and obesity seem to be the risk factors causing critical illness.

Understanding the clinical course of COVID-19 in the pregnant population is vital for deciding a suitable approach care for two patients; mother and fetus. Physiological alterations including pulmonary, cardiovascular and immunological alterations make it difficult to manage a pregnant patient [8]. It is important to know that pregnant patients with ARDS require care from the team work of experienced staff. During COIVID-19 pandemic, intensivists and obstetricians learned about the importance of close communication and making decisions together especially during delivery time; however, this decision process remains controversial.

We hope to contribute to this need, presenting the clinical features and six-months follow up of 17 pregnant patients who were infected with SARS-CoV-2 and admitted to the ICU. We aimed to explain clinical manifestations including invasive or non-invasive mechanical ventilation, prone positioning, medical and all other alternative therapies and laboratory findings.

Material and Methods

This is a retrospective, observational, single center study. In this study, those symptomatic pregnant patients were included who were admitted to the ICU between August 2020 and December 2021, with a positive result for SARS-CoV-2.After obtaining the approval of the ethics committee, with number 16.01.2023/1, the demographic, laboratory and clinical findings of those patients were recorded and at least a six-months follow-up after discharge of the mother and newborn was questioned.

Patients

This study included pregnant patients who had respiratory failure and ventilation requirements with a positive RT- PCR test result at different stage of the pregnancy trimester. Patients who were admitted to the ICU with an advanced oxygen demand (i.e. high flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV) or mechanical ventilation) were considered.

Statistical analysis

Normally distributed data are presented as the mean±standard deviation for numerical variables. The number of patients *(n)* and the proportions (%) were calculated for the categorical variables.

Results

A total of 17 patients were included in this study. Three of the patients died in the ICU, 13 patients were discharged, 1 patient is still being followed up in the palliative care unit. 14 of 17 patients required mechanical ventilation and 11 patients were extubated.

ICU period

The mean age of the patients was 31.8±4.6 years in surviving patients and 31.3±7.6 years in non-surviving patients. The mean body mass index (BMI) was 30.3±2.3 and 30.7±7.1 kg/m2 in surviving and non-surviving patients, respectively. No preexisting disease was found in 14 patients, whereas two patients had hypothyroidy and diabetes mellitus and one patient had hypertension and diabetes mellitus. Cough, dyspnea and myalgia were the symptoms that were most frequently reported by these patients. None of the patients had been vaccinated. The demo-biographic characteristics of these patients are presented in Table 1.

Six patients were nulliparous and others multiparous. Only one patient was in the second trimester, while all others were in the third trimester. The delivery gestation week was 32 weeks 6 days for surviving patients and 28 weeks 1 day for non-surviving patients. All patients had undergone cesarean section during the

ICU follow-up except two. One patient was discharged in the 27th week and delivered in term by cesarean section. Another pregnant patient was discharged in the 24th week, but she had cardiopulmonary arrest 5 days after her discharge. She was followed in the ICU until cesarean section in 33 weeks. Unfortunately, she had hypoxic ischemic encephalopathy and was tracheostomized in room air.

In 14 patients, invasive ventilation was required and all these intubated patients and except one who was in the second trimester had cesarean section in 24 hours after intubation. The average invasive ventilation time was 6.7±5.7 days in surviving patients and 22.6±3.2 days non-surviving patients. We applied prone position even before deliveryby supporting pregnancy belly to those who needed invasive ventilation and had PaO_2 / FiO_2 ratio under 150 or oxygen demand more than 60 % FiO_2. Three patients did not need invasive ventilation; they were stable with HFNC and NIMV. The average length of hospital stay was 25.5 ±6.6 days in surviving patients and 30.3±7.2 days in non-surviving patients. Three patients underwent immune plasma therapy; eight patients underwent treatment through remdesivir; nine patients underwent treatment through favipiravir; one patient underwent anakinra therapy. In two patients remdesivir therapy ceased because of increased liver enzymes. Fifteen patients underwent prednisolone pulse therapy, with 250 mg/day for three days.

In laboratory findings, we recorded aspartate transaminase (AST), C-reactive protein (CRP),

Table 1. Demo /biographic data of the patients and their newborns (mean SDwith median)

	Survival (n=14)	Non-survival (n=3)
Age(years)	31.8±4.6	31.3±7.6
Underlying diseases		
Diabetes Mellitus	4	None
Hypertension	1	None
Hypothyroidy	2	None
Coronary artery disease	None	1
Epilepsy	1	
BMI (kg/m2)	30.3±2.3	30.7±7.1
Parity		
Multiparous	9 2	2
Nulliparous	5 1	1
SARS-CoV-2 confirmative RT-PCR*	All	All
Gestational week on admission	30 weeks 4 days	27 weeks 1 day
Gestational week at birth	36 weeks 6 days	28 weeks 1 days
Birth weight (grams)	2034.6±772.2	1123.3±184.6
APGAR score (1st and 5th min)	1st6±2.3 5th 7.42±1.5	1st2±3.4 5th 3.6±3
SARS-CoV-2 confirmative RT-PCR	Four neonates have test with negative result	One neonate has test with negative result
NICU* stay (day)	27.2±22.9	101±40.5
Surviving newborn	13	3
Non-surviving newborn	1	

lactate dehydrogenase (LDH) and ferritin levels for all patients. High CRP and ferritin levels at admission were remarkable. When we analyzed these data with clinical findings, we could say interpret that the patients presented with macrophage activation syndrome. We performed thoracic tomography in 12 patients and multifocal ground glass opacities observed in 10 patients. In two patients we applied extracorporeal membrane oxygenation (ECMO). Unfortunately, neither of them survived. All clinical and laboratory findings are presented in Table 2.

Clinical course of newborns

A total of 16 neonates were admitted to the neonatal intensive care unit (NICU). The average birth weight of surviving newborns was 2034.6±777.2 g, while that of non-survivors was 1123±184.6 g. When the Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores of newborns were evaluated, the mean APGAR scores of survivorswere 6±2.3 and 7.4±1.5, while that of non-survivors was 2±3.4 and 3.6±3 for the first and fifth minutes. In the NICU, the length stay of babies of the surviving mothers was 27.2±22.9 days, while that of the non-surviving mothers was 101±40.5 days. All neonates survived and were discharged except the one whose mother who was in custody. We present the peripartum findings of the mother and fetus in Table 1.

Six months follow-up period

We had telephonic conversations with all patients at six months of recovery and none of them refused to answer our questions. Hence 13 patients agreed to participate, one surviving patient was still in the palliative care unit

Table 2. Clinical and laboratory findings

	Survival (n=14)	Non-survival (n=3)
Symptoms		
Dyspnea	10	2
Cough	12	3
Fever	3	None
Invasive ventilation (day)	6.7±5.7	22.6±3.2
Length of stay (day)	25.5±6.6	30.3±7.2
Prednisolone (250 mg/3 days)	13	2
Anti-viral therapy		
Remdesivir*	6	2
Favipiravir**	4	1
Ritonavir/Lopinavir	6	2
Immune plasma therapy	3	None
ECMO	None	2
CT Scan	n=9	n=1
Ground glass opacity	9	1
Embolism	None	None
Echocardiography	n=5 Normal findings	n=2 Normal findings
Laboratory findings on admission		
CRP (mg/L)	87.2 ±56	117±3.6
Lymphocyte (10^9/L)	0.81±0.39	0.6±0.3
LDH (u/L)	436±206	378±129.4
Ferritin (µ/L)	192.7±247.9	175±103.9
AST (u/L)	58.5±86.3	207.6±142.6

*In two patients remdesivir therapy was stopped because liver enzymes were elevated.

**If compassionate use of remdesivir was not available we applied favipiravir after delivery.

Table 3. Patients' findings on at least 6 months after recovery (number of patients=13)

	Yes (n)	No (n)
Cough	5	8
Dyspnea	2	11
Hospital admission	5	8
Re-COVID infection	2	11
COVID-19 vaccination mRNA vaccine Attenuated vaccine	 11 2	
Sleeping disorder	6	7
Psychiatric medication	1	12

at the time. Eight patients had no pulmonary symptoms during their daily activities. Five patients were admitted to the hospital with cough and myalgia after recovery and two were diagnosed tracheal stenosis and were hospitalized. All patients had been vaccinated with COVID-19 vaccines, 11 had mRNA vaccine and 2 had attenuated vaccines. Two patients had mild COVID-19 re-infection with no hospitalization. Six patients complained of fear of death and accompanying insomnia and anxiety, and one patient complained of claustrophobia. However, only one patient was found to be taking medication for depression.

Three patients were admitted to the hospital with complaints of cough and shortness of breath 1-3 weeks after discharge. One of them had a cardiopulmonary arrest in the emergency room. In the other 2 patients, stenosis was detected and underwent single-stage corrective surgery. We suspected stenosis during weaning from invasive ventilation in one another patient and had a CT scan. Tracheal stenosis was diagnosed and patient had surgery. On the phone call, three of them were asymptomatic, one was still in palliative unit, tracheostomized but in room air.

Discussion

Physiological changes in the respiratory and circulatory systems and alterations in immunology make pregnant patients more vulnerable to viral infections [8]. Pregnant patients are more susceptible to severe respiratory infections because of the reduction in total lung capacity and the inability to clear secretions especially in the third trimester [9]. A study of 91,412 women who tested positive for SARS-CoV-2 demonstrated that the most frequently reported symptoms were cough, shortness of breath and muscle pain. In the same study, substantially higher percentage of pregnant patients than nonpregnant patients was hospitalized and admitted to the ICU [10]. Centers for Disease and Prevention (CDC) reported that pregnant patients were three times likelier to be admitted to an ICU, 2.9 times likelier to need invasive ventilation and 1.7 times likelier to die compared to nonpregnant patients including over 400,000 persons of reproductive age with symptomatic COVID-19 and adjusted for age, race and ethnicity, and underlying medical conditions [6].

In pregnant patients, because of sufficient fetal oxygenation resting oxygen saturation should be above 95% for pulse oximetry monitoring. We admitted the patients who had dyspnea and oxygen demand more than 10 l/min with nonrebreather mask to achieve spO_2 >95. Three patients did not need invasive ventilation and adequate oxygen saturation was achieved with HFNC and NIMV. It is still not clear whether delivery improves maternal outcome. Because this timing of delivery is controversial and has to be done by a fetomaternal team, including an intensivist, obstetrician and neonatal intensivist. Certainly, fetal maturation is important; however, delivery before maternal decompensation can help a patient with respiratory failure. We did not wait for the progression of pregnant patient's respiratory distress and the mean delivery time was 31 weeks. We thought that not to wait for

delivery until maternal decompensation might be a good decision.

Prone positioning was routinely performed earlier after intubation in patients with PaO_2 / FiO_2ratio <150 and FiO_2>60% and was continued for about 16 hours in a day or more. By supporting the patient from appropriate points, the prone position can be applied safely in the second and third trimesters. Horrey and et al. clearly explained these supports in their study [11]. If the patient does not benefit from invasive ventilation and prone position (ECMO) should be considered [12]. In two patients, we set up ECMO, unfortunately neither survived.

We know that pregnant women especially those older than 35 years are usually in a hypercoagulable state, so current guidelines recommend that all pregnant women with confirmed COVID-19 should have thromboprophylaxis during the antenatal and postnatal period [12-14]. In our clinic all patients were treated with enoxaparin twice a day by calculating the dose according to weight, D-Dimer level and any risk factor.

In pregnant patients, there is a trend to use remdesivir and lopinavir-ritonavir for antiviral therapy. All patients who were hospitalized before admission to the ICU were treated with lopinavir-ritonavir. In the ICU, we preferred compassionate use of remdesivir in eight patients. However, because of the elevated liver enzymes in two patients, we had to discontinue it.

In late 2020, one year after the first case, US Food and Drug Administration approved messenger RNA (mRNA) vaccines for emergency use. However, there is not enough data about whether this vaccine has been approved to be used in pregnancy. The Royal College of Obstetricians and Gynecologists (RCOG) recommend vaccination without specification of gestation but if pregnant patients have a lower risk for severe disease, vaccination may be delayed until the second trimester [15]. In our study, none of the patients was vaccinated before or during pregnancy. After recovery, all of them chose to receive the COVID-19 vaccine, mRNA or attenuated vaccine. It is thought that COVID-19 vaccines may be beneficial in reducing the risk of severe disease and mortality in pregnant patients [16-17]. However, more research is needed for the approval of COVID-19 vaccines in pregnancy.

In the ICU, subglottic/tracheal stenosis or malaise are serious life-threatening conditions resulting from ischemia caused by intubation [18]. Prolonged duration of intubation time and prone position may facilitate the development of stenosis, especially in pregnant patients who have edematous upper airways. We found tracheal stenosis in our pregnant patients at a frequency that we had not seen in other patients who had undergone invasive ventilation and prone positioning. Tracheal stenosis should be kept in mind in patients who present with stridor or shortness of breath and have a history of intubation, and treatment of such patients should not be delayed.

The disadvantage of the most limiting aspect of the study was the small sample size and the absence of a control group.

Conclusion

While managing pregnant patients with respiratory failure, making decisions about delivery timing remains the most controversial. Based on our experience, we can say that if the week of gestation is compatible with life, the decision to deliver should be taken before severe progression of the mother's respiratory distress. Tracheal stenosis formation caused by intubation should be suspected even in short intubation periods in pregnant patients.

Informed Consent: The written informed consent was taken from participants and their parents.

Conflicts of interest: No potential conflict of interest was reported by the authors.

Funding: No funding was received for conducting this study.

Authors' Contributions: Concept: A.B., Design: A.B., Data Collection or Processing: F.A.B., G.A., D.Y., Analysis or Interpretation: İ.S., Literature Search: A.B., G.O., Writing: A.B.

References

1. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395:497–506.

2. Lokken EM, Huebner EM, Taylor GG et al. Disease severity, pregnancy outcomes, and maternal deaths

among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington State. *Am J Obstet Gynecol*. 2021;225(1):77. e1-77. e14.

3. DeBolt CA, Bianco A, Limaye MA et al. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. *Am J Obstet Gynecol*. 2021;224(5):510.e1-510.e12.

4. SoHee Kim, Choi Y, Lee Det al. Impact of COVID-19 on pregnant women in South Korea: Focusing on prevalence, severity, and clinical outcomes. *J Infect Public Health.* 2022 15(2):270-276.

5. Troiano H, Richter A, King C. Acute Respiratory Failure and Mechanical Ventilation in Women With COVID-19 During Pregnancy: Best Clinical Practices. *J Perinat Neonatal Nurs*. 2022;36(1):27-36.

6. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(44):1641-1647.

7. Lokken EM, Taylor GG, Huebner EM et al. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. *Am J Obstet Gynecol.* 2021;225(1): 75.e1-75e16.

8. Wastnedge EAN, Reynolds RM, van Boeckel SR, et al. Pregnancy and COVID-19. *Physiol Rev*. 2021; 101(1):303–318.

9. Goodnight WH, Soper DE. Pneumonia in pregnancy. *Crit Care Med*. 2005;33(10 Suppl):S390-S397.

10. Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(25):769-775.

11. Oxford-Horrey C, Savage M, Prabhu M et al. Putting It All Together: Clinical Considerations in the Care of Critically Ill Obstetric Patients with COVID-19. *Am J Perinatol*. 2020; 37(10):1044-1051.

12. Huang S, Zhao S, Luo H, et al. The role of extracorporeal membrane oxygenation in critically ill patients with COVID-19: a narrative review. *BMC Pulm Med.* 2021;21(1):116.

13. Kadir RA, Kobayashi T, Iba T, et al. COVID-19 coagulopathy in pregnancy: Critical review, preliminary recommendations, and ISTH registry-Communication from the ISTH SSC for Women's Health. *J Thromb Haemost*. 2020;18(11):3086-3098.

14. D'Souza R, Malhamé I, Teshler L, Acharya G, Hunt BJ, McLintock C. A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19. *Acta Obstet Gynecol Scand.* 2020;99(9):1110-1120.

15. The Royal College of Obstetricians and Gynaecologists. Coronavirus (COVID-19) vaccination in pregnancy. Information for healthcare professionals Version 16. Updated December 15, 2022. Accessed April 9, 2023. https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-women-s-health/coronavirus-covid-19-infection-in-pregnancy/

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Retrospective analysis of patients with cutaneous lupus erythematosus: A single-center experience

Sevgi Kulaklı[1]
Işıl Deniz Oğuz[1]

1. *Giresun University Faculty of Medicine, Department of Dermatology and Venereology, 28000, Giresun, Turkey*

Received: 31 December 2023
Accepted: 10 January 2024
Published: 31 January 2024

Corresponding Author: Sevgi Kulaklı, ORCID ID: 0000-0001-7886-1060

Giresun University, Faculty of Medicine, 28000, Giresun, Turkey

E-mail: sevgi.c@gmail.com

Abstract

Objective: Cutaneous lupus erythematosus (CLE) is a chronic inflammatory disease with different subtypes that exhibit variations in clinical, immunological, and prognostic features. This study aims to investigate the demographic and clinical characteristics of patients with CLE, the frequency of observed subtypes, antibody levels, the rate of co-occurrence with systemic lupus erythematosus (SLE), and the treatments administered.

Methods: The data of 56 patients diagnosed with CLE between November 2021 and December 2023 were retrospectively analyzed in this study. Demographic features, clinical findings, comorbidities, antinuclear antibody (ANA) and anti-dsDNA results, and treatments administered were recorded from patient files.

Results: The study included 38 females (67.9%) and 18 males (32.1%) with a mean age of 42.3±14.3 years. The most common clinical subtype was chronic CLE (CCLE) (85.7%). Within CCLE, discoid lupus erythematosus (DLE) constituted 76.8%. The most frequently affected anatomic region was the face. SLE was present in 16.1% of the patients. Among patients with acute CLE (ACLE), 100% had SLE, while this ratio was 66.7% for subacute CLE (SCLE) and 6.9% for DLE. ANA was positive in 42.9% of all patients and 32.6% of DLE patients.

Conclusion: In this study, it was observed that the most common clinical subtype was DLE, lesions most frequently occurred in the facial region, the highest risk of SLE was associated with ACLE, and the most commonly administered treatment was topical calcineurin inhibitors. Identifying the subtypes of CLE, initiating appropriate treatment, and regular monitoring of patients are crucial in the management of patients with CLE.

Keywords: Cutaneous Lupus Erythematosus, Discoid Lupus Erythematosus, Systemic Lupus Erythematosus, Antinuclear Antibody.

You may cite this article as: Kulaklı S, Oğuz ID. Retrospective analysis of patients with cutaneous lupus erythematosus: A single-center experience. *Cerasus J Med*. 2024; 1(1):27-34.

Introduction

Lupus erythematosus (LE) is an autoimmune disease that can manifest across a broad clinical spectrum, ranging from limited skin involvement to systemic disease affecting vital organs. Cutaneous lupus erythematosus (CLE) can present as an isolated skin disease or as one of the various clinical manifestations of systemic lupus erythematosus (SLE). Skin lesions in LE are categorized into lupus-specific and lupus non-specific. Non-specific lupus lesions, such as Reynaud phenomenon, vasculitis, livedo reticularis, and alopecia, often accompany SLE and may also occur in other diseases unrelated to LE [1,2]. Lupus-specific skin lesions are referred to as CLE, and they are further classified into four groups based on clinical, histopathological, and laboratory features: acute, subacute, intermittent, and chronic [3]. Differentiating between these clinical types is crucial due to variations in their frequencies, clinical, histopathological, and laboratory characteristics, rates of progression or co-occurrence to SLE, and treatments. The prevalence of CLE varies according to geographic regions, ethnic backgrounds, age, and gender [1-3].

This study aims to investigate the demographic and clinical characteristics of patients diagnosed with CLE in our region, the frequency of observed subtypes, antibody levels, the rate of co-occurrence with SLE, and the treatments administered.

Methods

Study population

The files of patients diagnosed with CLE between November 1, 2021, and December 1, 2023, at the Dermatology outpatient clinics of Giresun Training and Research Hospital were retrospectively examined. The following data were recorded from patient files: age, gender, duration of the disease, dermatological examination findings, number of lesions, CLE type, biopsy diagnosis, presence of accompanying SLE, accompanying systemic diseases, antinuclear antibody (ANA), anti-dsDNA results, and treatments administered. CLE types were categorized into four main groups: acute CLE (ACLE), subacute CLE (SCLE), intermittent CLE (ICLE)/lupus tumidus, and chronic CLE (CCLE). CCLE was further classified as discoid lupus erythematosus (DLE), lupus erythematosus profundus (LEP), verrucous lupus erythematosus, and chilblain lupus erythematosus (3). Patients with incomplete data in their files were not included in the study.

Statistical analysis

Statistical analyses were conducted using SPSS version 23 software. The data were presented as mean ± standard deviation, percentage, and count. Descriptive statistical methods were employed in the evaluation of the data. For the comparison of numerical data between two groups, the independent samples t-test was used when the assumption of normality was met; otherwise, the Mann-Whitney U test from non-parametric tests was employed. Depending on the situation, either the Chi-square test or Fisher's exact tests were used for the comparison of categorical data between the two groups. The Spearman correlation test was used to evaluate the correlation between parameters that did not exhibit a normal distribution. A p-value less than 0.05 was considered statistically significant.

Ethics approval

The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee of Giresun Training and Research Hospital (Approval number: 24, date: 18.12.2023).

Results

A total of 56 patients diagnosed with CLE were followed at the dermatology clinic between the specified dates. While the age ranged from 18 to 74, the mean age was 42.3±14.3 years. Of the patients, 38 were female (67.9%), and 18 were male (32.1%). The mean age at diagnosis was 39.8±15.35 years. The diagnosis was confirmed by histopathological examination in 54 of the 56 patients (96.4%). Two patients without a biopsy diagnosis had the clinical subtype of ACLE.

The most common clinical subtype was CCLE (48 patients, 85.7%). Among CCLE patients, 43 patients (76.8%) had DLE, 4 patients (7.2%) had chilblain lupus, and 1 patient (1.8%) had LEP. 3 patients (5.4%) had SCLE, 3 patients (5.4%) had lupus tumidus, and 2 patients (3.6%) had ACLE. Associated systemic diseases were present in 21 patients (37.5%). Among these, 10 had hypertension, 5 had diabetes mellitus,

5 had malignancy, 5 had thyroid disease, 3 had a connective tissue disease other than SLE (1 with rheumatoid arthritis, 1 with Sjögren's syndrome, 1 with mixed connective tissue disease), 2 had coronary artery disease, 1 had morphea, and 1 had chronic obstructive pulmonary disease. SLE was present in 16.1% of patients (9 patients). In patients with ACLE and LEP, 100% had SLE, in patients with SCLE, 66.7% had SLE, in patients with chilblain lupus erythematosus, 25% had SLE, and in patients with DLE, 6.9% had SLE. Of the patients with CLE, 32 (57.1%) were ANA negative, and 24 (42.9%) were ANA positive (11 with 1/80, 5 with 1/160, 6 with 1/320, and 2 with >1/320 titers). ANA positivity was observed in 100% of patients with ACLE, LEP, and chilblain lupus, 66.7% of patients with SCLE, 33.3% of patients with lupus tumidus, and 32.5% of patients with DLE. Eight patients (14.3%) had positive anti-dsDNA. Anti-dsDNA positivity was observed in all patients with ACLE and LEP, 66.7% of patients with SCLE, 25% of patients with chilblain lupus, and 4.6% of patients with DLE. Treatment modalities included topical calcineurin inhibitors (TCI) in 18 patients, hydroxychloroquine (HQ) in 14 patients, HQ and systemic steroids in 9 patients, topical/intralesional corticosteroids in 6 patients, topical corticosteroids and calcineurin inhibitor combination in 6 patients, HQ and azathiopyrin in 2 patients, and systemic isotretinoin in 1 patient. The demographic, clinical, laboratory, and treatment characteristics of all patients are shown in Table 1.

In our study population, the most common clinical subtype was DLE (76.8%). The mean age of DLE patients, including 28 females (65.1%) and 15 males (34.9%), was 44.9±13.28 years. The mean age at diagnosis was 42.32±14.48 years. While 11 patients (25.6%) had a single lesion, 32 patients (74.4%) had multiple lesions. The most common location of the lesions was the face (55.8%), followed by the scalp (37.2%). The cheek was the most common facial area affected (27.9%). At least one systemic disease was present in 41.9% of patients. The most common accompanying systemic disease was hypertension (20.9%). SLE diagnosis was present in 3 patients (7%). ANA was positive in 14 patients (32.6%), with titers of 1/80 in 9 patients, 1/160 in 3 patients, and 1/320 in 2 patients. Anti-dsDNA was positive in 2 patients (4.7%). The most commonly prescribed treatment for patients with DLE was TCI (41.9%), followed by HQ (27.9%). The demographic, clinical, laboratory, and treatment characteristics of patients with DLE are shown in Table 2.

There was no significant difference between female and male patients with DLE in terms of age (p=0.387), age at diagnosis (p=0.264), lesion number (p=0.905), localization (p=0.062), frequency of accompanying systemic diseases (p=0.64), presence of accompanying SLE (p=0.541), ANA positivity (p=0.415), anti-dsDNA positivity (p=0.535), and treatments administered (p=0.991) (Table 2).

There was no significant difference between individuals with single or multiple DLE lesions in terms of age (p=0.535), age at diagnosis (p=0.89), presence of accompanying SLE (p=0.558), ANA positivity (p=0.311), anti-dsDNA positivity (p=0.985), and treatments administered (p=0.526).

Discussion

Lupus erythematosus encompasses a wide clinical spectrum, ranging from a serious systemic disease to localized disease confined to the skin, characterized by chronic inflammatory processes with relapses and remissions. The most commonly affected organs are the skin, joints, and kidneys. Skin lesions observed in LE are divided into lupus-specific and lupus non-specific categories [4]. Lupus-specific skin lesions, termed CLE, are further classified into four groups: acute, subacute, intermittent (lupus tumidus), and chronic. These groups, which differ clinically, histopathologically, and immunologically, also exhibit varying rates of association with SLE. While numerous studies have investigated the epidemiological, clinical, and laboratory characteristics of patients with SLE, there is limited research specifically focusing on CLE [1,2].

In our study, the majority of patients were diagnosed with CCLE (85.7%). Among the CCLE subtypes, the most commonly observed clinical type was DLE (76.8%). Other CCLE subtypes included LEP in 1 patient (1.8%), and chilblain LE in 4 patients (7.2%). The prevalence of DLE in our study is consistent with a retrospective evaluation of 186 LE patients, where DLE was the most frequent CLE type (72.5%). In that study, the frequencies of SCLE and ACLE were 8%

Table 1. The demographic, clinical, laboratory characteristics, and treatments of patients with cutaneous lupus erythematosus

	CLE (n=56)	CCLE (n=48)	SCLE (n=3)	Lupus tumidus (n=3)	ACLE (n=2)
Age, years (mean±SD)	42.3±14.3	42.6±14.3	40.3±22.2	46.3±10.9	32.5±10.6
Sex					
Female, n (%)	38 (67.9)	32 (66.7)	2 (66.7)	2 (66.7)	2 (100)
Male , n (%)	18 (32.1)	16 (33.3)	1 (33.3)	1 (33.3)	-
Age at diagnosis, years, (mean±SD)	39.8±15.35	40.25±15.03	39.67±23.12	46±11.27	19.5±7.78
Localisation of lesions, n (%)					
Face	28 (50)	24 (50)	-	2 (66.7)	2 (100)
Scalp	16 (28.6)	16 (33.3)	-	-	-
Trunk	2 (3.6)	-	1 (33.3)	-	-
Face, neck, upper limbs	2 (3.6)	1 (2.09)	2 (66.7)	-	-
Face, ears	1 (1.8)	1 (2.09)	-	-	-
Face, trunk, upper limbs	1 (1.8)	1 (2.09)	-	-	-
Face, neck	1 (1.8)	1 (2.09)	-	-	-
Upper and lower limbs	3 (5.4)	3 (6.25)	-	-	-
Upper lims	1 (1.8)	-	-	1 (33.3)	-
Lower limbs	1 (1.8)	1 (2.09)	-	-	-
Number of lesions, n (%)					
Single	12 (21.43)	12 (25)	-	-	-
Multiple	44 (78.57)	36 (75)	3 (100)	3 (100)	2 (100)
SLE					
Present	9 (16.1)	5 (10.42)	2 (66.7)	-	2 (100)
Absent	47 (83.9)	43 (89.58)	1 (33.3)	3 (100)	-
ANA					
Negative	32 (57.1)	29 (60.42)	1 (33.3)	2 (66.7)	-
1/80	11 (19.6)	11 (22.93)	-	-	-
1/160	5 (8.9)	4 (8.3)	1 (33.3)	-	-
1/320	6 (10.7)	3 (6.25)	1 (33.3)	1 (33.3)	1 (50)
>1/320	2 (3.6)	1 (2.1)	-	-	1 (50)

Anti-dsDNA					
Negative	48 (85.7)	44 (91.7)	1 (33.3)	3 (100)	-
Positive	8 (14.3)	4 (8.3)	2 (66.7)	-	2 (100)
Treatment					
TCI	18 (32.1)	18 (37.5)	-	-	-
TCS/ILCS	6 (10.7)	6 (12.5)	-	-	-
TCS+TCI	6 (10.7)	5 (10.42)	-	1 (33.3)	-
HQ	14 (25)	13 (27.08)	-	1 (33.3)	-
HQ + systemic steroid	9 (16.1)	4 (8.3)	3 (100)	1 (33.3)	1 (50)
HQ + AZA	2 (3.6)	1 (2.1)	-	-	1 (50)
Systemic isotretinoin	1 (1.8)	1 (2.1)	-	-	-

Abbreviations: CLE, cutaneous lupus erythematosus; CCLE, chronic cutaneous lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; ACLE, acute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; ANA, antinuclear antibody; anti-dsDNA, anti-doublestrandedDNA; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; ILCS, intralesional corticosteroids; HQ, hydroxychloroquine; AZA, azathioprine; SD, standard deviation.

Table 2. The demographic, clinical, laboratory characteristics, and treatments of patients with discoid lupus erythematosus

	Female (n=28)	Male (n=15)	Total (n=43)	p
Age, years (mean±SD)	43.6±12.95	47.3±14	44.9±13.28	0.387†
Age at diagnosis, years, (mean±SD)	40.5±14.85	45.7±13.6	42.32±14.48	0.264†
Localisation of lesions, n (%)				0.062¶
Face	18 (64.28)	6 (40)	24 (55.8)	
Scalp	10 (35.72)	6 (40)	16 (37.2)	
Face, ears	-	1 (6.66)	1 (2.3)	
Face, trunk, upper limbs	-	1 (6.66)	1 (2.3)	
Face, neck	-	1 (6.66)	1 (2.3)	
Number of lesions, n (%)				0.905§
Single	7 (25)	4 (26.66)	11 (25.6)	
Multiple	21 (75)	11 (73.33)	32 (74.4)	
SLE				0.541¶
Present	3 (10.72)	-	3 (7)	
Absent	25 (89.28)	15 (100)	40 (93)	

ANA				0.415¶
Negative	18 (64.29)	11 (73.33)	29 (67.4)	
1/80	7 (25)	2 (13.33)	9 (20.9)	
1/160	1 (3.57)	2 (13.33)	3 (7)	
1/320	2 (7.14)	0	2 (4.7)	
AntidsDNA				0.535¶
Negative	26 (92.86)	15 (100)	41 (95.3)	
Positive	2 (7.14)	-	2 (4.7)	
Treatment				0.991¶
TCI	12 (42.86)	6 (40)	18 (41.9)	
TCS/ILCS	2 (7.14)	1 (6.66)	3 (7)	
TCS+TCI†	3 (10.72)	2 (13.33)	5 (11.6)	
HQ	7 (25)	5 (38.46)	12 (27.9)	
HQ + systemic steroid	2 (7.14)	1 (6.66)	3 (7)	
HQ + AZA	1 (3.57)	-	1 (2.3)	
Systemic isotretinoin	1 (3.57)	-	1 (2.3)	

Abbreviations: SLE, systemic lupus erythematosus; ANA, antinuclear antibody; anti-dsDNA, anti-doublestrandedDNA; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; ILCS, intralesional corticosteroids; HQ, hydroxychloroquine; AZA, azathioprine; SD, standard deviation. † Independent samples t test, ‡ Mann-Whitney U test, ¶ Fisher exact test, § Pearson chi-square test. P<0.05 is statistically significant. Bold values sign statistical significance.

and 15%, respectively [5]. Another series of 156 CLE patients reported DLE as the most common clinical type (82.7%), with 14.74% diagnosed with SCLE and 0.64% with ACLE [6]. In a multicenter study involving 1002 CLE patients, 39.62% had DLE, 30.34% had ACLE, 23.55% had SCLE, and 6.48% had lupus tumidus [7]. Our study aligns with these findings, highlighting DLE as the most prevalent CLE subtype, consistent with existing literature.

In our study, the female-to-male ratio for CLE was determined to be 2.1. Various studies have reported this ratio to range between 1.79 and 4.31 [4,6,7]. The mean age of disease onset in these studies was between 40 and 43 years, a range consistent with the mean onset age in our study. CLE lesions are more frequently observed on sun-exposed areas of the skin, particularly the head, neck, and arms [1]. In a study by Izquerdo et al., it was reported that CLE lesions most commonly occurred on the head and neck and it was observed that DLE and ACLE lesions were most commonly located on the head and neck, while SCLE lesions predominantly affected the trunk [4]. Similarly, our study revealed that CCLE lesions were most frequently located on the face, followed by the scalp.

In our study, SLE was present in 16.1% of the patients. In the literature, the rate of concurrent or subsequent SLE in CLE patients has been reported to be between 12.18% and 40.7% in different studies [6-8]. ACLE is the subtype of CLE with the highest risk of developing systemic disease [9]. Although the number of patients diagnosed with ACLE was quite small in our study, in line with the literature, all of these patients had a diagnosis of SLE, and they were positive for both ANA and anti-dsDNA.

In our study, 37.5% of the patients had concomitant systemic diseases. Among them, 10 patients had hypertension, 5 had diabetes mellitus, 5 had malignancy, 5 had thyroid disease, 3 had connective tissue diseases other than SLE, 2 had coronary artery disease, 1 had morphea, and 1 had chronic obstructive pulmonary disease. It has been shown that individuals with CLE are more likely to have autoimmune diseases (other than SLE) compared to the general population, with

Hashimoto's thyroiditis and Sjögren's syndrome being the most commonly associated autoimmune diseases [10]. While the increased risk of cancer is known in chronic autoimmune diseases, studies with isolated CLE patients, such as Singh et al.'s study involving 155 patients, did not find such a risk [11]. Conversely, in a larger series of CLE patients by Westermann et al., an increased risk of non-Hodgkin lymphoma, pancreas, lung, and ovarian cancer was demonstrated [12]. In our study, 1 patient had testis, 1 had breast, 1 had lung, 1 had thyroid, and 1 had colon and prostate cancer. The occurrence of associated malignancies may be coincidental, and these results need to be supported by more extensive studies involving a larger population of CLE patients. The most common concomitant systemic disease in our study was hypertension (17.8%). In a previous study, hypertension was reported to be the most common comorbidity with DLE at 18.2%, followed by diabetes mellitus at 6.8% [13]. Since diabetes mellitus and hypertension are common diseases in the middle-aged population, further extensive studies are needed to determine whether there is a significant association with DLE.

In our study, the majority of patients were DLE, while the number of patients in other clinical subtypes was quite low. Consistent with the literature, the average age at diagnosis for our patients was approximately 41, and females received about 2 times more DLE diagnoses than males [14]. It is rare for DLE lesions to involve the trunk without affecting the upper face and scalp, and when lesions are present below the neck, it is referred to as generalized DLE [15]. While localized DLE is more frequently observed (60-80%), generalized DLE is less common (20-40%) [15,16]. In our study, only one patient (2.32%) had generalized DLE. It is known that generalized DLE has a higher likelihood of progressing to SLE compared to localized DLE [15,17]. However, in our study, the patient with generalized DLE did not have SLE. Among the three DLE patients diagnosed with SLE, localized DLE in the head region was present in all cases.

The positivity of ANA has been shown to be significant in patients with DLE, serving as a potential indicator of progression to SLE in previous studies [13,17]. In various previous studies, ANA positivity in DLE patients has been reported at rates ranging from 16.1% to 67% [18,19]. In our study, ANA positivity was detected in 32.5% of patients with DLE, while all patients who developed SLE had a positive ANA (2 patients at 1/320, 1 patient at 1/160).

Treatment options for CCLE include topical corticosteroids, intralesional corticosteroids, TCI, and HQ as first-line therapies. In cases resistant to these treatments, a combination of HQ and systemic steroids, systemic isotretinoin, thalidomide, dapsone, methotrexate, mycophenolate mofetil, and other agents can be applied [3]. In our study, the most commonly used treatment was TCI, followed by HQ.

The main limitations of our study include its retrospective nature and being a single-center study, and a limited number of patients with clinical types other than DLE.

Conclusion

CLE is a rare skin disease with different clinical and immunological characteristics, exhibiting subtypes that vary in their association with or progression to SLE. As lesions often affect sun exposed areas of the skin, the most common subtype, DLE can lead to atrophy, scarring, and permanent hair loss, impacting the quality of life [14,17]. Therefore, determining the subtypes of the disease, initiating appropriate treatment, and regularly monitoring patients are of great importance. Our study revealed that DLE is the most frequently observed clinical type, with lesions predominantly affecting the facial region. The highest risk for SLE was associated with the ACLE, and the most commonly applied treatment was TCI. These findings reflect the demographic, clinical, and immunological features of CLE patients in our region, contributing to the literature in this regard.

Conflicts of interest: The authors declare there is no conflicts of interest.

Funding: None.

Authors' Contributions: Concept: S.K., Design: S.K., Data Collection or Processing: S.K., I.D.O., Analysis or Interpretation: S.K., I.D.O., Literature Search: S.K., Writing: S.K.

References

1. Vale ECSD, Garcia LC. Cutaneous lupus erythematosus: a review of etiopathogenic, clinical, diagnostic and therapeutic aspects. *An Bras Dermatol.* 2023;98(3):355-372.

2. Niebel D, de Vos L, Fetter T, Brägelmann C, Wenzel J. Cutaneous Lupus Erythematosus: An Update on Pathogenesis and Future Therapeutic Directions. *Am J Clin Dermatol.* 2023;24(4):521-540.

3. Lu Q, Long H, Chow S, et al. Guideline for the diagnosis, treatment and long-term management of cutaneous lupus erythematosus. *J Autoimmun.* 2021;123:102707.

4. Avilés Izquierdo JA, Cano Martínez N, Lázaro Ochaita P. Epidemiological characteristics of patients with cutaneous lupus erythematosus. *Actas Dermosifiliogr.* 2014;105(1):69-73.

5. Cardinali C, Caproni M, Bernacchi E, Amato L, Fabbri P. The spectrum of cutaneous manifestations in lupus erythematosus--the Italian experience. *Lupus.* 2000;9(6):417-423.

6. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. *Arch Dermatol.* 2009;145(3):249-253.

7. Biazar C, Sigges J, Patsinakidis N, et al. Cutaneous lupus erythematosus: first multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE). *Autoimmun Rev.* 2013;12(3):444-454.

8. Chong BF, Song J, Olsen NJ. Determining risk factors for developing systemic lupus erythematosus in patients with discoid lupus erythematosus. *Br J Dermatol.* 2012;166(1):29-35.

9. Filotico R, Mastrandrea V. Cutaneous lupus erythematosus: clinico-pathologic correlation. *G Ital Dermatol Venereol.* 2018;153(2):216-229.

10. Lin TL, Wu CY, Juan CK, et al. Long-Term Risk of Autoimmune Diseases other than Systemic Lupus Erythematosus in Cutaneous Lupus Erythematosus-Alone Patients: A 10-Year Nationwide Cohort Study. *Dermatology.* 2022;238(1):92-100.

11. Singh AG, Crowson CS, Singh S, et al. Cancer risk in cutaneous lupus erythematosus: a population-based cohort study. *Rheumatology (Oxford).* 2016;55(11):2009-2013.

12. Westermann R, Zobbe K, Cordtz R, Haugaard JH, Dreyer L. Increased cancer risk in patients with cutaneous lupus erythematosus and systemic lupus erythematosus compared with the general population: A Danish nationwide cohort study. *Lupus.* 2021;30(5):752-761.

13. Yavuz GO, Yavuz IH, Bayram I, Aktar R, Bilgili SG. Clinic experience in discoid lupus erythematosus: a retrospective study of 132 cases. *Postepy Dermatol Alergol.* 2019;36(6):739-743.

14. Uva L, Miguel D, Pinheiro C, Freitas JP, Marques Gomes M, Filipe P. Cutaneous manifestations of systemic lupus erythematosus. *Autoimmune Dis.* 2012;2012:834291.

15. Cooper EE, Pisano CE, Shapiro SC. Cutaneous Manifestations of "Lupus": Systemic Lupus Erythematosus and Beyond. *Int J Rheumatol*. 2021;2021:6610509.

16. Zhou W, Wu H, Zhao M, Lu Q. New insights into the progression from cutaneous lupus to systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2020;16(8):829-837.

17. Al-Saif FM, Al-Balbeesi AO, Al-Samary AI, et al. Discoid lupus erythematosus in a Saudi population: Clinical and histopathological study. *JSSDDS.* 2012;16:9-12.

18. Tang WYM, Chan LY, Lo KK. Discoid lupus erythematosus in Hongkong Chinese: a review of 12 cases. *HKMJ.* 1996;2(3):239-245.

19. Cenk H, Gökşin Ş, İmren IG. Diskoid Lupus Eritematozus Hastalarının Klinikoepidemiyolojik Profili ve Sistemik Hastalıklarla İlişkisi.*Turk J Clin Lab.* 2022;13(2):207-214.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Distribution of pathogens of respiratory tract infections by months and age groups

Mediha UĞUR[1]
Ahmet Melih ŞAHİN[2]

1. *Asst. Prof., MD, Department of Clinical Microbiology, Giresun Training and Research Hospital*

2. *Asst. Prof., MD, Department of Clinical Microbiology and Infectious Diseases, Giresun Training and Research Hospital*

Received: 22 December 2023
Accepted: 11 January 2024
Published: 31 January 2024

Corresponding Author: Mediha UĞUR, ORCID ID: 0000-0002-2526-397X

Department of Clinical Microbiology, Giresun University Faculty of Medicine, Giresun 28100, Turkey

E-mail: medihacerrah@hotmail.com

Abstract

Objective: Respiratory tract infections are a significant public health problem worldwide. The aim of this study is rapidly identify respiratory tract infection pathogens, classify them according to months and age groups, development of appropriate treatment recommendations according to pathogen and age.

Methods: Patients with a pathogen in their respiratory tract panels between September 2022 –March 2023 have been included in the study. Samples for respiratory tract panel were studied on QIAstat-Dx Analyzer 1.0 (Qiagen®, Hilden, Germany) device with QIAstat-Dx® Respiratory SARS-CoV-2 Panel kit. Results of six months were evaluated retrospectively.

Results: A total of 557 pathogens were found in 437 patients among 576 inpatients whose respiratory tract panel has been requested. The most frequently seen agent was determined as rhinovirus/enterovirus (25.13%) and the most frequent co-occurrence was determined to be rhinovirus/enterovirus - respiratory syncytial virus (RSV). The most frequently seen pathogen in September, October, January and February was rhinovirus/enterovirus while RSV was the most frequent agent in November and December.

Conclusion: Respiratory tract infection pathogens were analyzed a six-month period, and the highest positivity rate was detected in December. The 1-18 age range was the group in which the highest number of pathogens were detected. And the fact that RSV positivity in <1 age group was at high rates (51.58%) is important. Very short detection time for viral pathogens thanks to molecular methods in 75.86% of patients, who have been hospitalized due to respiratory tract infection with panel testing done, is considered to contribute in reducing improper use of antibiotics.

Keywords: Respiratory Tract Infection, Viral Infections, RSV

You may cite this article as: Uğur M, Şahin AM. Distribution of pathogens of respiratory tract infections by months and age groups. *Cerasus J Med.* 2024;1(1):35-41.

Introduction

Acute respiratory infections account for a large proportion of all acute morbidity and mortality worldwide [1]. As viral pathogens cause disease at a rate of 80%, they also rank high among the list of reasons of improper use of antibiotics. The main viral pathogens are influenza virus, respiratory syncytial virus (RSV), coronavirus, adenovirus and rhinovirus [1]. Viral respiratory tract infections increase especially common in autumn-winter months. The disease is self-limiting in individuals while they cause morbidity and mortality in vulnerable individuals. These infections are among significant causes of hospitalization especially in pediatric and geriatric patients [2,3].

Distinguishing between viral and bacterial causes in respiratory tract infections is only possible through laboratory diagnosis since clinic symptoms specific to viral pathogens are very few [4].

Real-time polymerase chain reaction (RT-PCR) tests with high sensitivity which give results in shorter periods and which can identify coinfections are preferred rather than classical virology diagnosis tests such as routine laboratory virus culture, hemagglutination inhibition test, enzyme-linked immuno sorbent assay test and immunofluorescence test. Respiratory tract viruses may be identified with high sensitivity and specificity through RT-PCR and thus enabling prevention of unnecessary antibiotics usage [3,5].

Accurate and rapid identification of viral pathogens is quite important for estimating the course of illness, implementing the proper treatment, reducing mortality and morbidity rates, stopping epidemics and reducing unnecessary use of antibiotics [1]. Knowing which virus is an agent other than bacterial and viral distinction would provide information about the progress of illness and the risk of pneumonia. The progress of illness, and thus the treatment approach vary depending on age groups and the pathogens [6]. Fast and correct identification of the agent through molecular methods plays a key role in the correct treatment.

Our study analyzes the six-month period in autumn-winter seasons in which viral respiratory tract infection outbreaks increased. The aim was to implement the right antiviral treatment through early detection of agents by determining the distributions of pathogens by months and age groups and to prevent unnecessary antibiotic usage by ending empirically initiated antibiotic treatment.

Methods

The study has obtained the approval of the ethical board with the ethical board decision number 22.05.2023/07 from Giresun Training and Research Hospital Clinical Research Ethics Committee. The study included patients with identified respiratory tract infections in the 6-month period between September 2022-March 2023. Samples obtained from patients who were hospitalized for respiratory tract infectionswere sent to laboratory to be studied on with QIAstat-Dx Analyzer 1.0 (Qiagen®, Hilden, Germany) device and QIAstat-Dx® Respiratory SARS-CoV-2 Panel kit. Panel kit identifies SARS-CoV-2 and 21 additional pathogens (Influenza A, Influenza A subtype H1N1/2009, Influenza A subtype H1, Influenza A subtype H3, Influenza B, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory syncytial virus A/B, human Metapneumovirus A/B, Adenovirus, Bocavirus, Rhinovirus/Enterovirus, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Bordetella pertussis*). Results of six-month period were assessed retrospectively. Distribution of infection pathogens by months and age ranges was analyzed.

Results

Among 576 inpatients whose respiratory tract panel tests were requested in the six-month period, 557 pathogens were identified in 437 patients. 238 patients were male and 199 patients were female and their mean ages were 14.10± 23.56, 20.57±28.17. There were 90 patients below the age of one, 237 patients between 1-18, 65 patients between 18-65 and 45 patients over 65. 41.11% of the patient group under the age of 1 were intensive care patients together with 23.63% of the patient group of 1-18, 12.31% of the patient group of 19-65 and 48.89% of the patient group over 65. Respiratory tract panel positivity rate was determined as 75.86%. Among 437 patients, one pathogen was identified in 332 patients (75.97%), two pathogens were identified in 92 patients (21.05%), three pathogens were identified in 11 patients (2.52%)

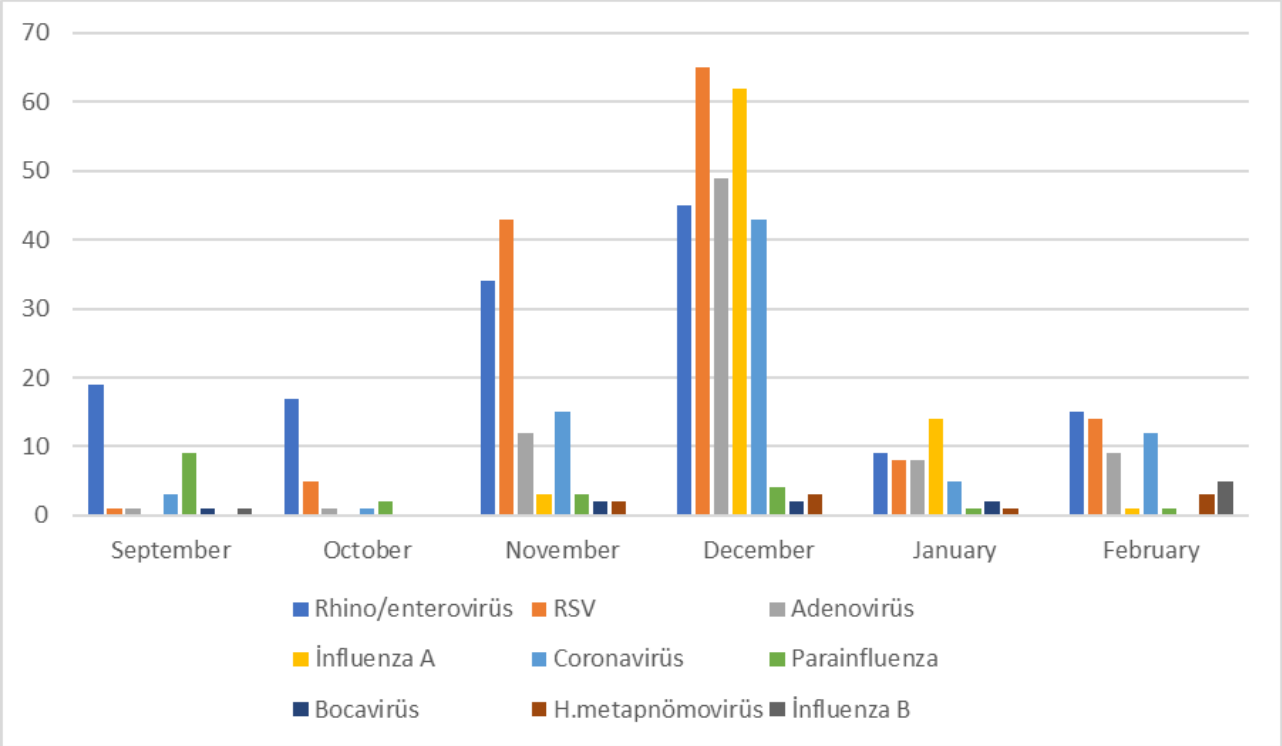


Figure 1: Distribution of pathogens of respiratory tract infection by months

Table 1. Distribution of pathogens of respiratory tract infection by age groups

Pathogens	<1 (%)	1-18 (%)	19-65 (%)	>65 (%)	Total
Rhinovirus/Enterovirus	34 (26.98)	82 (26.28)	15 (21.43)	9 (18.37)	140 (25.13)
RSV*	65 (51.58)	56 (17.95)	5 (7.14)	10 (20.41)	136 (24.42)
Adenovirus	6 (4.76)	69 (22.11)	3 (4.29)	2 (4.08)	80 (14.36)
Influenza A H3	1 (0.79)	41 (13.14)	15 (21.43)	4 (8.16)	61 (10.95)
Coronavirus OC43	10 (7.93)	19 (6.09)	1 (1.43)	5 (10.20)	35 (6.28)
SARS-CoV-2	1 (0.79)	4 (1.28)	20 (28.57)	15 (30.61)	40 (7.18)
Parainfluenza	5 (3.97)	11 (3.52)	3 (4.29)	1 (2.04)	20 (3.59)
Influenza A H1N1	0	13 (4.17)	3 (4.29)	1 (2.04)	17 (3.05)
Bocavirus	0	6 (1.92)	1 (1.43)	0	7 (1.26)
Human metapneumovirus	3 (2.38)	4 (1.28)	1 (1.43)	1 (2.04)	9 (1.62)
Human coronavirus NL63	1 (0.79)	3 (0.96)	0	0	4 (0.72)
Influenza A	0	1 (0.32)	0	1 (2.04)	2 (0.36)
Influenza B	0	3 (0.96)	3 (4.29)	0	6 (1.08)
Total agents	126	312	70	49	557
Number of patients	90 (20.59)	237 (54.23)	65 (14.87)	45 (10.30)	437
INTENSIVE CARE	37 (41.11)	56 (23.63)	8 (12.31)	22 (48.89)	123 (28.15)
SERVICE	53	181	57	23	314

*Respiratory syncytial virus

and four pathogens were identified in 2 patients (0.46%). The most frequent pathogen was identified as rhinovirus/enterovirus (25.13%) and most frequently seen coinfections were rhinovirus/enterovirus-RSV (19.11%). The most frequent pathogen in September, October, January and February was rhinovirus/enterovirus (54.29%, 65.38%, 18.75%, 25%) while the most frequent pathogen in November and December was RSV (37.72%, 23.81%). 273 (49.01%) of the total 557 pathogens were identified in the month of December. Distribution of pathogens by months is presented in Figure 1. The most frequent pathogen among the patient group under the age of one was revealed to be RSV (51.58%) while it was rhinovirus/enterovirus in 1-18 age group (26.28%), SARS-CoV-2 in 18-65 and over 65 age groups (28.57%), (30.61%). Distribution of pathogens by age groups is presented in Table 1. Polymicrobial pathogens were identified in 32 of patients under the age of one (35.55%), 63 of the patients in 1-18 age group (26.58%), 6 of the patients in 18-65 age group (9.23%) and 4 of the patients over 65 (8.88%).

Discussion

Although the clinical findings of bacterial and viral respiratory tract infections are similar, their treatment approaches are different. Timely and correct diagnosis of respiratory tract pathogens is important especially to prevent unnecessary use of antibiotics and antibiotic resistance [7]. Various studies have shown that unnecessary antibiotic usage is at a quite high level in treatment of respiratory tract infections [8-10]. Unnecessary use of antibiotics leads to increased cost as well as contributing in the development of antibiotic resistance [11]. Moreover, it should be noted that antibiotics are not innocent pharmaceuticals, and they may have serious side effects [12]. In this study, panel test was requested from 576 patients who were hospitalized due to respiratory tract infection and 437 of these (75.86%) were revealed to have one or more viral pathogens. This significantly high-rate points at the smart utilization of the test as well as the fact that most of the respiratory tract infections are caused by viral pathogens.

The most frequently identified rhinovirus/enterovirus is the most common reason of upper respiratory tract infections (URTIs) across the world and almost throughout the year and it peaks especially in autumn and spring months [13]. The pathogen which is considered to be the cause of relatively innocent URTIs is associated with chronic obstructive pulmonary diseases exacerbations, development of asthma, sever bronchiolitis in infants and children, and fatal pneumonia in elderly and adults with suppressed immune systems [14,15]. In our study, rhinovirus/enterovirus was identified throughout all months, but it was observed to constitute the majority of agents especially in September (54.28%) and October (65.38%). Although observed in all age groups, rhinovirus is the most common respiratory tract virus among children under the age of five and it is the leading cause of hospitalization for children under the age of two. And it is reportedly the second pathogen, following RSV, for hospitalizations due to bronchiolitis [14,16]. In a study conducted on children hospitalized due to acute respiratory tract infection in Croatia, it was determined that rhinovirus was the most common virus detected in individuals under 18 years of age, 60.4% monoinfection and 39.6% coinfection with other respiratory viruses [16]. In our study, rhinovirus was observed the most among the age group of 1-18 and the pathogen was identified as monoinfection in 59.29% (83) of the patients and as coinfection in 49.01% (57) of the patients.

The study identified RSV as the most frequent pathogen in November and December in line with many other studies [15,16]. When pathogen distribution by age groups is examined, RSV was the most frequently identified pathogenin <1 age group (51.58%). The most important cause of childhood lower respiratory tract infections (LRTIs) is respiratory tract viruses, and the most frequent pathogen is RSV. It is estimated that global mortality rate attributed to RSV-related LRTIs in small children is as high as 150,000 per year [17,18]. It is reported that 2.1 million outpatient treatments and more than 57.500 hospitalizations occur every year in children below the age of five in relation to RSV infections in the U.S. [19]. According to the findings of an extensive study, approximately 33 million RSV-related acute LRTI cases, 3,6 million RSV-related acute LRTI hospitalizations and 26,300 hospital deaths occur every year across the world. 13,300 cases of deaths are reported to be among 0-6-month old infants [20]. Şık et al. identified RSV as the most frequently

seen pathogen in their study conducted on the patients in pediatric intensive care unit [21]. As an pathogen which is frequently identified in the early years of life, RSV is also known as a common and very severe respiratory tract pathogen among 65 year-olds and older individuals [22]. In a multi-centered prospective study, multi pathogen infections with rhinovirus and RSV were identified in 30% of the children hospitalized due to respiratory tract infection [23]. In our study, RSV was identified as monoinfection at the rate of 64.7% and the highest coinfection rate of 19.11% was determined with rhinovirus/enterovirus. The studies show that the most common coinfection is rhinovirus-RSV coinfection [24,25].

Adenovirus may cause infections at all ages, however it is most commonly identified among pediatric population, especially among small children and infants [26]. In our study, adenovirus was identified in 80 patients and most frequently among individuals in the age group of 1-18 (86.25%). In a study conducted by Chen et al. on children below the age of 14, yearly pathogens of respiratory tract infections were analyzed and a significant increase in adenovirus was identified in 2018-2019. Although it has shown a decrease in 2020-2021 in the post-COVID-19 period, 80% of the cases were reported to have been hospitalized [27]. And 59.6% of the cases during an epidemic identified in the U.S. in 2013–2014 were reported to be below the age of 18, and 68.7% of all cases were reportedly hospitalized while 31.6% received treatment in the intensive care unit [28]. 93.75% of adenovirus cases being seen in children under the age of 18 and coinfection having a high rate of 50% are important facts in terms of mortality and morbidity of infection.

Influenza outbreaks which typically start as of the end of October in the Northern hemisphere peak between December-February and continue up until May [29]. Influenza is rarely identified in autumn in the study and a dramatic increase is observed in the month of December. Influenza virus infections generally limit themselves with URTIs while they are also associated with LRTIs especially among elderly people with the possibility of a mortal course of disease. Individuals below the age of one and above the age of 65 are in the most vulnerable age group against the virus and vaccination is recommended for this group [30,31]. In our study, only 7 individuals were diagnosed with this pathogenin the patient group of below the age of one and above the age of 65, and however, the fact that 5 of those received intensive care treatment (71.43%) shows the importance of the pathogen in these age groups. Influenza B viral infections generally lead to localized outbreaks while influenza A virus is a primary pathogen for human infections and thus it is the main reason for epidemics and pandemics [1]. Two subtypes of influenza A which are still in circulation are A (H1N1) and A (H3N2) [31]. According to the data of our country's Weekly Influenza (Flu) Surveillance Report, influenza A H3 virus has the highest rate of 62% of all influenza cases of 2022-2023 [32]. According to the analysis of six-month data in our study, 70.9% of 86 influenza cases in total are observed to be Influenza A H3. According to the data of the Weekly Influenza (Flu) Surveillance Report, the distribution of the cases similar to Influenza virus positive flu by age groups shows that the highest case rate is among the age group of 5-14 [32].

Coronavirus infections generally increase in autumn and winter months across the world [33,34]. Four-season coronavirus strain may cause common cold symptoms in people, and it is responsible of 15-30% of respiratory tract infections each year. The most frequent strain among these was identified as OC43-CoV [16]. In our study, OC43-CoV was identified as the most frequent seasonal coronavirus other than SARS-CoV-2 and NL63-CoV was identified in very few numbers.

Distribution of pathogens of respiratory tract infections identified via molecular method was analyzed in the study for a six-month period covering autumn and winter seasons. Distribution of respiratory tract pathogens by seasons and age groups was similar in our country to the global data. The fact that 78.6% of the pathogens were identified in individuals below the age of 18 shows that children are more at risk in terms of respiratory tract infections compared to other age groups. Especially the high rate of intensive care hospitalizations of infants below the age of 1 due to respiratory tract infections (41.11%) shows the importance of fast and correct diagnosis of respiratory tract viruses in the first year of life and early childhood period and this is possible with molecular methods. Early detection in very short times such as 1 hour is possible with molecular methods for

patients who go to the hospital for respiratory tract infection and are hospitalized due to the severity of their clinical conditions. Identification of positivity in 75.86% of samples and all of it having viral pathogens are important information to be able to prevent empirical antibiotic usage in this patient group.

Conclusion

Knowing that viral agents are so common in respiratory tract infections, which involve the most frequent unnecessary uses of antibiotics, should be instructive for clinicians in terms of initiating empirical antibiotic treatment. Moreover, the use of PCR on the right patients will enable fast identification of the pathogens as well as their proper treatments.

Financial support and sponsorship: There are no financial support and sponsorship.

Conflict of interest: There are no conflicts of interest.

Ethical considerations: The study has obtained the approval of the ethical board with the ethical board decision number 22.05.2023/07 from Giresun Training and Research Hospital Clinical Research Ethics Committee.

Author contribution: Concept: M.U., A.M.Ş., Design: M.U., A.M.Ş., Data Collection or Processing: M.U., A.M.Ş., Analysis or Interpretation: M.U., A.M.Ş., Literature Search: M.U., A.M.Ş., Writing: M.U., A.M.Ş.

References

1. Zhang N, Wang L, Deng X, et al. Recent advances in the detection of respiratory virus infection in humans. *J Med Virol*. 2020;92(4):408–417.

2. Hawkes MT, Lee BE, Robinson JL. Seasonality of Respiratory Viruses at Northern Latitudes. *JAMA Netw Open*. 2021;4(9):e2124650.

3. Huang HS, Tsai CL, Chang J, Hsu TC, Lin S, Lee CC. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. *Clin Microbiol Infect*. 2018;24(10):1055-1063.

4. Kanberoğlu Gİ, Güdeloğlu E, Bağ Ö, Ecevi ÇÖ. Akut alt solunum yolu enfeksiyonu nedeniyle hastaneye yatan çocuklarda Multiplex-PCR ile saptanan enfeksiyöz etkenlerin değerlendirilmesi. *Pamukkale Tıp Derg*. 2021;14(3):604-610

5. Alp A, Taşçı O, Ergin A, Köseoğlu Eser Ö. Evaluation of the Respiratory Viral Panel PCR Test Results Before and After COVID-19 Pandemic. *Mikrobiyol Bul*. 2022;56(4):667-681.

6. Aktaş F. Inn:Willke Topçu A, Söyletir G, Doğanay M (eds). Enfeksiyon Hastalıkları ve Mikrobiyolojisi. 4th ed. İstanbul, 2017:719-720.

7. Huang E, Wang Y, Yang N, Shu B, Zhang G, Liu D. A fully automated microfluidic PCR-array system for rapid detection of multiple respiratory tract infection pathogens. *Anal Bioanal Chem*. 2021;413(7):1787–1798.

8. Plachouras D, Kärki T, Hansen S, et al. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use 2016 to 2017. *Euro Surveill*. 2018;23(46):1800393.

9. Walsh T.L, Taffe K, Sacca N, et al. Risk Factors for Unnecessary Antibiotic Prescribing for Acute Respiratory Tract Infections in Primary Care. *Mayo Clin Proc Innov Qual Outcomes*. 2020;4(1):31-39.

10. Havers FP, Hicks LA, Chung JR, et al. Outpatient antibiotic prescribing for acute respiratory infections during influenza seasons. *JAMA Netw Open.* 2018;1(2): e180243.

11. Sur D.K.C, Plesa M.L. Antibiotic Use in Acute Upper Respiratory Tract Infections. *Am Fam Physician.* 2022;106(6):628-636.

12. Wawruch M, Bozekova L, Krcmery S, Kriska M. Risks of antibiotic treatment. *Bratisl Lek Listy*. 2002;103(7-8):270-275.

13. Jacobs SE, Lamson DM, George K, Walsha TJ. Human Rhinoviruses. *Clin Microbiol Rev*. 2013;26(1):135–162.

14. Olofsson S, Brittain-Long R, Andersson LM, Westin J, Lindh M. PCR for detection of respiratory viruses: seasonal variations of virus infections. *Expert Rev Anti Infect Ther*. 2011;9(8):615–626.

15. García-Arroyo L, Prim N, Del Cuerpo M, et al. Prevalence and seasonality of viral respiratory infections in a temperate climate region: A 24-year study (1997–2020). *Influenza Other Respir Viruses*. 2022;16(4):756–766.

16. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of Respiratory Viral Infections. *Annu Rev Virol.*2020;7(1):83-101

17. Gümüş HH, Yarkın F, Alt Solunum Yolu Enfeksiyonu Olan Çocuklarda Respiratory Syncytial Virus (RSV) Enfeksiyon İnsidansının Araştırılması. *Dicle Med J*. 2022;49(1):176-186.

18. Bulut Ö, Kahraman K, Uçar Ç, Ovalı F. Assessment Of Cases Admıtted To The Neonatal Intensıve Care Unıt Wıth Lower Respıratory Tract Infectıon. *Kocatepe Medical Journal*. 2022;23:75-81.

19. Smith D.K, Seales S, Budzik C, Respiratory Syncytial Virus Bronchiolitis in Children. *Am Fam Physician*. 2017;95(2):94-99.

20. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet.* 2022;399(10340):2047-2064.

21. Şık G, Demirbuğa A, Annayev A, Cabiri A, Delice E, Çıtak A. Çocuk Yoğun Bakım Ünitesinde Alt Solunum Yolu Enfeksiyonu Tanısıyla Yatan Hastalarda Viral Patojen Sıklığı ve Hastaların Klinik Özellikleri. *J Pediatr Inf*. 2020;14(1):27-32.

22. Griffiths C, Drews SJ, Marchanta DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. *Clin Microbiol Rev*. 2017; 30(1):277-319.

23. Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med*. 2012;166(8):700-706

24. Meskill S.D, O'Bryant S.C. Respiratory Virus Co-infection in Acute Respiratory Infections in Children. *Curr Infect Dis Rep*. 2020;22(1):3.

25. Derrar F, Izri K, Kaddache C, Boukari R, Hannoun D. Virologic study of acute lower respiratory tract infections in children admitted to the pediatric department of Blida University Hospital, Algeria. *New Microbes and New Infect*. 2019;30:100536.

26. Shieh W.J. Human adenovirus infections in pediatric population -An update on clinico-pathologic correlation. *Biomed J*. 2022;45(1):38-49.

27. Chen Y, Lin T, Wang C. B, et al. Human adenovirus (HAdV) infection in children with acute respiratory tract infections in Guangzhou, China, 2010–2021: a molecular epidemiology study. *World J Pediatr*. 2022;18(8):545–552.

28. Kendall Scott M, Chommanard C, Lu X, et al. Human Adenovirus Associated with Severe Respiratory Infection, Oregon, USA, 2013–2014. *Emerg Infect Dis*. 2016;22(6):1044-1051.

29. Nypaver C, Dehlinger C, Carter C. Influenza and Influenza Vaccine: A Review. *J Midwifery Women's Health*. 2021;66(1):45-53.

30. Mifsud EJ, Kuba M, Barr IG. Innate Immune Responses to Influenza Virus Infections in the Upper Respiratory Tract. *Viruses*. 2021;13(10):2090.

31. Çakır N, Durusu Tanrıöver M. Flu and Beyond: The Burden of Adult Influenza Infections and Benefits from Influenza Vaccination. *FLORA*. 2022;27(3):353-362.

32. T.C. SAĞLIK BAKANLIĞI Halk Sağlığı Genel Müdürlüğü Bulaşıcı Hastalıklar ve Erken Uyarı Dairesi Başkanlığı. Sentinel ILI Sürveyansı, 2022-2023. Haftalık İnfluenza (Grip) Sürveyans Raporu 2023/8. Hafta (20 – 26 Şubat 2023). 2023, ANKARA.

33. Çolak M, Aktaş Tapısız A, Güzel Tunçcan Ö, Bozdayı G. Retrospective Evaluation of the Prevelance and Seasonal Distribution of Coronaviridae Positivity Before the COVID-19 Pandemic (2016-2020). *FLORA*. 2020;25(4):480-489.

34. Park S, Lee Y, Michelow IC, Choe YJ. Global seasonality of human coronaviruses: a systematic review. *Open Forum Infect Dis*. 2020;7:ofaa443.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Uric acid / albumin ratio in acute kidney injury developing in intensive care unit: A case control study

Ebru Canakci[1]
Mehmet Şerif Alp[2]
Yunus Emre Güven[3]
Şükran İçöz[4]

1. Ordu University Faculty of Medicine, The Department of Anesthesiology and Reanimation, Ordu, Türkiye
2. Ordu University Faculty of Medicine, The Department of Anesthesiology and Reanimation, Ordu, Türkiye
3. Ordu University Faculty of Medicine, The Department of Anesthesiology and Reanimation, Ordu, Türkiye
4. Ordu University Faculty of Medicine, The Department of Anesthesiology and Reanimation, Ordu, Türkiye

Received: 25 December 2023
Accepted: 11 January 2024
Published: 31 January 2024

Corresponding Author: Ebru Canakci, ORCID ID: 0000-0003-2093-9229
Ordu University Faculty of Medicine, The Department of Anesthesiology and Reanimation, Ordu, Türkiye
E-mail: canakciebru@gmail.com

The abstract of this study was presented as an oral presentation at the 28th National Congress of Thoracic Cardiovascular Anesthesia and Intensive Care, 23-25 September 2022 ,Manisa,Turkey.

Abstract

Objective: Various scoring systems and markers are used in intensive care practice, and molecules which can predict mortality and change the course of treatment continue to be researched. We aimed to investigate whether uric acid, albumin, uric acid/albumin ratio and uric acid/creatinine ratio were associated with mortality in intensive care cases.

Materials and Methods: Our study was designed retrospectively and involved 600 cases. The uric acid and albumin values of the cases were recorded at the time of admission were recorded, and the uric acid/albumin ratio and uric acid/creatine ratio were calculated. APACHE-II scores and SOFA scores of all the patients at the time of admission were recorded.

Results: Uric acid, uric/albumin ratio, uric acid/creatinine ratios of Groups AKI and Non-AKI were statistically significant ($p<0.001$, $p<0.001$, $p<0.001$, respectively). When exitus and discharged cases were compared, albumin and uric acid/albumin ratios were statistically significant ($p<0.050$, $p<0.050$, in order). The cut-off value for albumin was found as 2.75. Mortality increases at the values below 2.75. A meaningful difference was detected between the distributions of albumin cut-off value according to the last condition of the patients ($p=0.038$). We discovered a notable correlation between albumin, uric acid/creatinine ratio, APACHE-II, SOFA scores ($p=0.045$; $p=0.012$; $p=0.018$; $p=0.020$, respectively).

Conclusion: Uric acid/albumin ratio may be a useful biomarker in predicting prognosis in cases of acute kidney injury. We believe that our study will shed light on future studies on the uric acid/albumin ratio in larger populations and different patient groups.

Keywords: Intensive care, mortality, uric acid, uric acid albumin ratio, uric acid creatinine ratio

You may cite this article as: Canakci E, Alp MŞ, Güven YE, İçöz Ş. Uric acid / albumin ratio in acute kidney injury developing in intensive care unit: A case control study.*Cerasus J Med.* 2024;1(1):42-51.

Introduction

Today, there has been an increase in the need for intensive care as a result of prolonged life expectancy and increased chronic/acute diseases. As a result of this increasing need, medical developments in intensive care are accelerating and reduction of intensive care mortality is put forward as the main objective [1]. Various scoring systems and markers are used in intensive care practice, and molecules which can predict mortality and change the course of treatment continue to be researched. The ideal marker should be cheap and easy to use in daily practice [2,3]. Serum uric acid level can be used to predict intensive care mortality since it meets these criteria and reflects the antioxidant capacity in plasma [4].

Uric acid emerges as the last result of purine metabolism in the human body. Plasma uric acid level is influenced by many factors, and the main reason for the change in uric acid value is overproduction or changes in renal functions. Changes can be observed in uric acid levels resulting from decreased glomerular filtration, renal hypoperfusion, decreased tubular reabsorption and elimination [5]. Even though there were slight differences in the normal uric acid value, it was considered 3.4-7.2 mg/dl in males and 2.4-6.1 mg/dl in females [6]. In the last century, people's uric acid threshold have increased with the changing lifestyle and the relationship of this situation with existing diseases has been reviewed in many different studies. It has been demonstrated in different studies that enhanced uric acid levels are in related to atherosclerosis, hypertension, adiposity, coronary heart diseases, diabetes mellitus, stroke, and malignancy [7].

The results of the studies are in contradiction with each other, and the relevance thereamong uric acid and mortality has not been revealed with certainty. Additionally, there are not enough studies investigating the correlation among uric acid value and period of mechanical ventilation requirement, non-intensive care mortality, re-hospitalization rates, and the need for hemodialysis. Again, the existing scoring systems, which are Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment Score (SOFA), are used in the intensive care of our hospital, and there are no studies examining the relationship of these scoring systems with uric acid in the literature.

For this reason, in our study, we aimed at revealing the relationship of uric acid values, uric acid/albumin ratio, and uric acid/creatine ratios of the patients, who were hospitalized to our intensive care unit between January, 2017 –September, 2019, at the time of hospitalization with whether patients had hemodynamic instability, and especially mortality, and comparing them with existing intensive care scoring systems in the prognostic terms.

Materials and Methods

Ethical consent was gained from the Ordu University Clinical Research Ethics Committee for our study (Date: 10/10/2019 Decision Number: 2019/139). The files of the patients who were admitted to Ordu University Education and Research Hospital Anesthesia Reanimation Intensive Care Unit 1 and 2 between January 1, 2017 and September 30, 2019 were retrospectively examined. The data of the patients were collected through intensive care files and the hospital operating system. 600 cases were included in the study. Among whole subjects admitted to the intensive care unit between the given dates, 300 intensive care patients with acute kidney injury and 300 intensive care patients without acute kidney injury were added in the study. Patients below 18 years of age, patients with malignancy, and patients using drugs that may increase uric acid levels (such as ethambutol and pyrazinamide) were excluded from the study. Patients with underlying diseases such as nephrotic syndrome, liver cirrhosis, 2nd and 3rd degree burns, which might affect the plasma albumin levels, were excluded from the study. Hypoalbuminemia was described as plasma albumin level below 3.5 g/dL. Hyperuricemia, on the other hand, was described as plasma uric acid level higher than 7 mg/dL. Demographic data of the patients such as age, gender, underlying diseases, and duration of stay in our intensive care unit were recorded. Acute kidney injury (AKI) has been defined conveniently the guidelines of the kidney disease improving global outcomes (KDIGO) [8,9]. If the serum creatinine heighten was ≥0.3 mg/dL within 48 hours according to KDIGO criteria or if the increase in basal creatinine value was ≥1.5 times within 7 days; or if urinary output was <0.5 ml/kg/hour in the last 6 hours, a diagnosis of acute kidney injury was established [9]. As intensive care scoring systems, APACHE-II and

SOFA scores were calculated. Routine biochemical values, uric acid levels, albumin, CRP (C-Reactive Protein), procalcitonin values of the patients during hospitalization were recorded. The uric acid/albumin, uric acid/creatinine ratios of each case were calculated.

Statistical Analysis

The data were analyzed using IBM SPSS v23. Compliance with normal distribution was examined with Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi-square test was applied to compare categorical variables according to groups. In the comparison of quantitative variables by binary groups, the Independent two-sample t test was used for data with normal distribution, and the Mann-Whitney U test was performed for data without normal distribution. Spearman's rho correlation coefficient was used to examine the relationship between quantitative variables without normal distribution. According to the exitus condition, ROC (Receiver operating curve) analysis was used to determine the cut-off value for albumin, uric acid and uric acid/albumin. The results of the analysis were presented as mean ± standard deviation and median (minimum – maximum) for the quantitative data, and as frequency (percent) for categorical data. The level of significance was taken as $p<0.05$.

Table 1. Comparison of the categorical variables according to the groups

	AKI [n=300]	Non-AKI [n=300]	Total	Test Statistics	P
Gender					
Female	110 [36.7]	140 [46.7]	250 [41.7]	χ^2= 0.617	0.432
Male	190 [63.3]	160 [53.3]	350 [58.3]		
Comorbidity					
Diabetes Mellitus	0 [0]	1 0 [3.4]	10 [1.7]		
Hypertension	30 [10]	20 [6.9]	50 [8.5]		
Congestive Heart Failure	20 [6.7]	10 [3.4]	30 [5.1]		
COPD*	10 [3.3]	40 [13.8]	50 [8.5]	χ^2= 13.820	0.054
Cerebro-Vascular Disease	20 [6.7]	100 [34.5]	120 [20.3]		
Mixed Etiology	170 [56.7]	70 [24.1]	240 [40.7]		
Malignancy	40 [13.3]	40 [13.8]	80 [13.6]		
Solitary Kidney	10 [3.3]	0 [0]	10 [1.7]		
Last condition					
Exitus	170 [56.7]	110 [36.7]	280 [46.7]	χ^2=2.411	0.121
Discharged	130 [43.3]	190 [63.3]	320 [53.3]		
Mechanical Ventilation					
No	70 [23.3]	60 [20]	130 [21.7]	χ^2=0.098	0.754
Yes	230 [76.7]	240 [80]	470 [78.3]		
Hemodialysis					
No	120 [46.2]	300 [100]	420 [75]	χ^2=21.538	**<0.001**
Yes	140 [53.8]	0 [0]	140 [25]		
Proteinuria					
No	190 [63.3]	290 [96.7]	480 [80]	χ^2=10.417	**0.001**
Yes	110 [36.7]	10 [3.3]	120 [20]		

x^2: Chi-square test statistics [*]: Chronic Obstructive Pulmonary Disease

Table 2. Comparison of quantitative variables according to the groups

	AKI [n=300]	Non-AKI [n=300]	Total	Test statistics	p
Age	73.97 ± 11.65 77 [48 - 90]	100.21 ± 154.52 77 [20 - 899]	86.86 ± 108.49 77 [20 - 899]	U=424.0	0.867
Total hospitalization days	12.63 ± 13.04 8.5 [3 - 51]	25.3 ± 27.8 13 [3 - 105]	18.97 ± 22.46 10 [3 - 105]	U=325.0	0.064
BUN	95.61 ± 48.76 84.65 [31.2 - 203.8]	27.42 ± 9.93 25.55 [11.3 - 47.3]	61.52 ± 48.98 41.9 [11.3 - 203.8]	U=27.0	**<0.001**
Creatine	4.33 ± 1.71 3.9 [1.59 - 8.35]	0.81 ± 0.21 0.84 [0.45 - 1.24]	2.57 ± 2.14 1.42 [0.45 - 8.35]	t=11.203	**<0.001**
Glucose	186.93 ± 84 187 [72 - 317]	169.73 ± 73.49 155.5 [70 - 381]	178.33 ± 78.73 162.5 [70 - 381]	U=400.0	0.460
Calcium [Ca]	7.9 ± 1.24 7.85 [5.6 - 10.5]	8.1 ± 0.89 8.3 [5.1 - 9.2]	8 ± 1.08 8.05 [5.1 - 10.5]	t=-0.705	0.484
Sodium [Na]	131.86 ± 5.17 132 [119 - 140]	139.03 ± 6.81 138.5 [129 - 158]	135.51 ± 7.01 135 [119 - 158]	U=168.5	**<0.001**
Potassium [K]:	5.35 ± 1.15 5.2 [3 - 8.39]	3.85 ± 0.75 3.8 [2.33 - 5.27]	4.58 ± 1.22 4.58 [2.33 - 8.39]	U=88.5	**<0.001**
Albumin [Alb]	2.68 ± 0.53 2.65 [1.9 - 3.6]	2.81 ± 0.39 2.9 [2 - 3.6]	2.74 ± 0.46 2.75 [1.9 - 3.6]	t=-1.083	0.284
Procalcitonin	14.34 ± 33.86 1.72 [0.13 - 155]	10.62 ± 18.94 1.63 [0.06 - 84.4]	12.48 ± 27.26 1.72 [0.06 - 155]	U=435.0	0.824
C-Reactive Protein [CRP]	19.04 ± 14.08 15.15 [1.52 - 45.8]	14.47 ± 10.96 10.4 [2.7 - 42]	16.76 ± 12.72 13.95 [1.52 - 45.8]	U=386.5	0.348

t: Independent two-sample t test, U: Mann-Whitney U test, mean ± s. deviation, median [minimum - maximum]

Results

The comparison of categorical variables according to the groups is given in Table 1.

The comparison of quantitative variables according to the groups is given in Table 2.

Comparison of other quantitative variables according to groups is presented in Table 3.

A meaningful difference was detected between the medians of the BUN and creatinine values according to the groups (p<0.001, p<0.001). Similarly, there is a meaningful difference between the medians of Na, K values according to the groups (p<0.001, p<0.001). There is a meaningful difference between the medians of PH values, HCO3 values, BEecf values according to the groups (p<0.001, p<0.001, p<0.001). Again similarly ,there is a meaningful difference between the medians of uric acid values, uric acid/albumin ratio values, uric acid/creatinine values according to the groups (p<0.001,p<0.001,p<0.001). The comparison of albumin, uric acid, uric acid/albumin ratio and mean arterial pressure values according to the last condition of the patients are presented in Table 4.

There is a meaningful difference between the mean values of albumin, uric acid/albumin ratio and mean arterial pressure according to the last condition of the patients [p=0.05; p=0.05; p=0.005, respectively]. The average of exitus cases was obtained as 66.88, and the

Table 3. Comparison of quantitative variables according to the groups [continued]

	AKI	NON-AKI	Total	Test statistics	p
APACHE-II score	21.17 ± 7.41 21 [6 - 36]	18.63 ± 6.78 20 [8 - 35]	19.9 ± 7.16 20 [6 - 36]	t=1.382	0.172
SOFA score	8.57 ± 3.23 8 [4 - 16]	7.37 ± 2.77 6.5 [4 - 14]	7.97 ± 3.05 7 [4 - 16]	U=342.0	0.108
PH	7.23 ± 0.22 7.3 [6.81 - 7.51]	7.44 ± 0.11 7.46 [7.1 - 7.6]	7.33 ± 0.2 7.4 [6.81 - 7.6]	U=161.5	**<0.001**
PO2	99.69 ± 42.52 93.85 [10 - 228]	101.79 ± 36.94 91.1 [40.3 - 194]	100.74 ± 39.5 92.75 [10 - 228]	U = 431.0	0.779
PCO2	41.04 ± 12.29 36.95 [23.9 - 76.1]	40.25 ± 9.67 38.3 [21 - 67.7]	40.64 ± 10.97 38.15 [21 - 76.1]	U=421.0	0.668
HCO3	18.16 ± 6.7 20.95 [5.4 - 28.1]	40.39 ± 68.25 27.5 [12 - 399.2]	29.27 ± 49.37 23.1 [5.4 - 399.2]	U=170.5	**<0.001**
SO2	94.91 ± 5.23 96.65 [81.5 - 100]	95.86 ± 6.57 97.25 [63.5 - 100]	95.39 ± 5.91 97.05 [63.5 - 100]	U=386.5	0.348
BEecf	-8.67 ± 9.52 -4.7 [-28.9 - 4]	2.65 ± 14.1 3.45 [-52 - 19.1]	-3.01 ± 13.22 -1.8 [-52 - 19.1]	U=177.5	**<0.001**
Uric acid	6.65 ± 0.7 6.84 [5.23 - 8]	4.73 ± 0.59 4.74 [3.9 - 5.9]	5.69 ± 1.16 5.65 [3.9 - 8]	U=19.5	**<0.001**
Uric acid / albumin ratio	2.56 ± 0.47 2.55 [1.82 - 3.57]	1.73 ± 0.41 1.65 [1.11 - 2.8]	2.14 ± 0.6 2.03 [1.11 - 3.57]	t = 7.302	**<0.001**
Uric acid / Creatine ratio	1.82 ± 0.82 1.53 [0.83-3.71]	6.16 ± 1.68 5.75 [3.8 - 11.15]	3.99 ± 2.55 3.76 [0.83 - 11.15]	U=0.0	**<0.001**
MAP [Mean Arterial Pressure]	73.37 ± 17.29 73.33 [46.67 - 113.33]	72.23 ± 14.25 73.33 [50 - 100.67]	72.8 ± 15.72 73.33 [46.67 - 113.33]	t=0.277	0.783

t: Independent two-sample t test, U: Mann-Whitney U test, mean ± s. deviation, median [minimum - maximum]

average of discharged cases was 77.98. This difference results from the fact that the mean arterial pressure average of those who died was lower than the average of those who were discharged.

The consequences of the ROC analysis for uric acid/albumin ratio, albumin and uric acid according to the exitus status are given in Table 5.

The cut-off value for albumin was found as 2.75. Mortality increases with values below 2.75. When the cut-off value for albumin was taken as 2.75, the area under the curve (AUC) was found as 0.653. This value is statistically significant (p=0.042). When the cut-off value was taken as 2.75, the sensitivity was obtained as 64.3% and the specificity as 62.5%. No significant cut-off values were obtained for uric acid/albumin ratio and uric acid (p>0.050).

ROC curves drawn for uric acid/albumin ratio, albumin and uric acid according to the exitus status of the cases are demonstrated Figure 1, Figure 2 and Figure 3.

The comparison of the albumin cut-off values of the AKI and Non-AKI group and in accordance with the exitus status is presented in Table 6.

Table 4. Comparison of albumin, uric acid, uric acid/albumin ratio, uric acid/creatinine ratio and mean arterial pressure values according to the last condition of the patients

	Exitus	Discharged	Total	Test statistics	P
Albumin	2.62 ± 0.5 2.6 [1.9 - 3.6]	2.85 ± 0.41 2.9 [2 - 3.6]	2.74 ± 0.46 2.75 [1.9 - 3.6]	t=-1.982	**0.05**
Uric acid	5.82 ± 1.16 5.9 [3.9 - 8]	5.57 ± 1.17 5.35 [3.99 - 7.9]	5.69 ± 1.16 5.65 [3.9 - 8]	U=405.0	0.524
Uric acid / albumin ratio	2.3 ± 0.64 2.26 [1.37 - 3.57]	2 ± 0.54 1.93 [1.11 - 3.32]	2.14 ± 0.6 2.03 [1.11 - 3.57]	t=1.973	**0.05**
Uric acid/creatinine ratio	3.5 ± 2.37 2.82 [0.84 - 8.65]	4.42 ± 2.66 4.51 [0.83 - 11.15]	3.99 ± 2.55 3.76 [0.83 - 11.15]	U=361.0	0.197
Mean Arterial Pressure	66.88 ± 13.27 65.83 [46.67 - 100.67]	77.98 ± 16.05 80 [50 - 113.33]	72.8 ± 15.72 73.33 [46.67 - 113.33]	t=-2.894	**0.005**

t: Independent two-sample t test, U: Mann-Whitney U test, mean ± s. deviation, median [minimum - maximum]

Table 5. ROC analysis results for uric acid/albumin ratio, albumin and uric acid according to exitus status

	AUC [95% CI]	P	SH	Cut-off value	Sensitivity	Specificity
Uric acid / albumin ratio	0.647 [0.506 - 0.788]	0.051	0.072	≥2.0313	0.607	0.594
Albumin	0.653 [0.51 - 0.796]	**0.042**	0.073	≤2.75	0.643	0.625
Uric acid	0.548 [0.399 - 0.697]	0.524	0.076	≥5.65	0.571	0.562

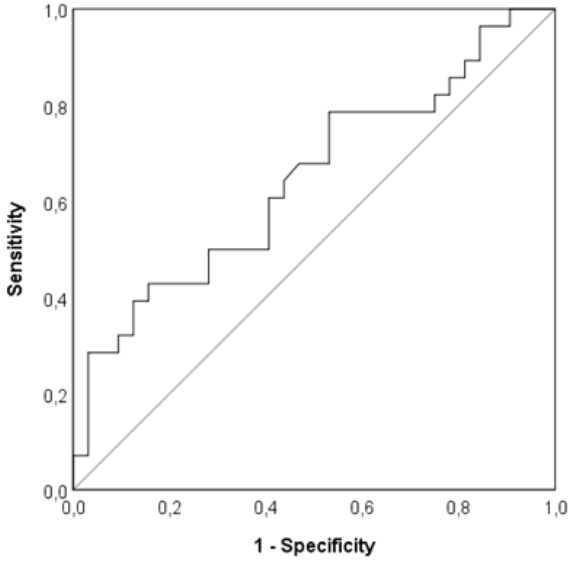


Figure 1. ROC curve for Uric acid/albumin ratio according to the exitus status

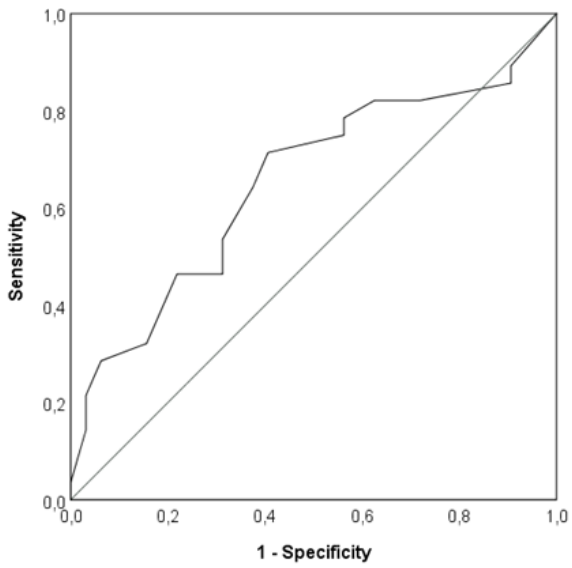


Figure 2. ROC curve for albumin according to the exitus status

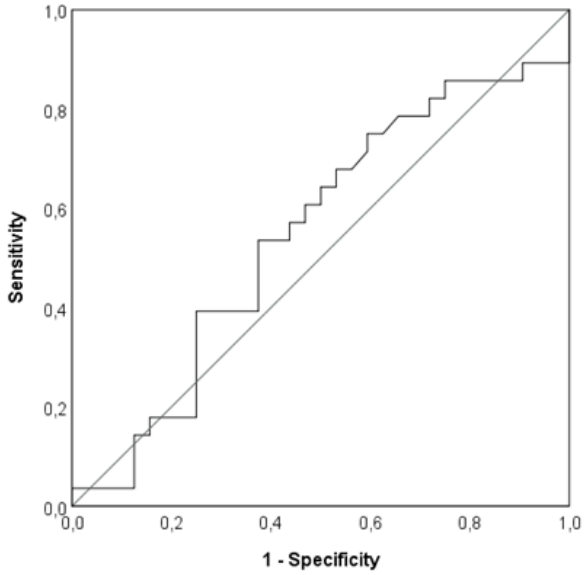


Figure 3. ROC curve for Uric acid according to the exitus status

Table 6. Comparison of the albumin cut-off value according to groups and exitus status

	≤2.75	>2.75	Total	Test statistics	P
Group					
AKI	170 [56.7]	130 [43.3]	300 [100]	χ^2=1.067	0.302
NON-AKI	130 [43.3]	170 [56.7]	300 [100]		
Last condition					
Discharged	120 [37.5]	200 [62.5]	320 [100]	χ^2=4.286	**0.038**
Exitus	180 [64.3]	100 [35.7]	280 [100]		

x^2: Chi-square test statistics

There was a meaningful difference between the distributions of the albumin cut-off value according to the last condition of the patients (p=0.038). While the albumin value of 64.3% of exitus cases was obtained as 2.75 and below, the albumin value of 62.5% of discharged cases was found above 2.75. No meaningful difference between the distributions of the albumin cut-off value according to the groups (when AKI and Non-AKI groups are compared) (p>0.050).

Discussion

When uric acid values were confronted among the AKI and Non-AKI groups, a meaningful difference was detected; the uric acid values were found to be higher in the AKI group. When the uric acid/albumin values were compared between the AKI and Non-AKI groups, a meaningful difference was found. The uric acid/albumin ratio was found to be considerably higher in the AKI group. When uric acid/creatinine values were compared between the AKI and Non-AKI groups, a meaningful difference was found. The uric acid/creatinine ratio was found to be considerably low in the AKI group. When compared in terms of mortality, no relationships were found among uric acid, uric acid/creatinine proportion and mortality. However, meantime the relationship between albumin, uric acid/albumin proportion and mean blood pressure and mortality were compared, a significant relationship was found. As the uric acid/albumin ratio increases, mortality increases. It is possible to say that mortality increases as albumin and mean blood pressure decrease.

Recently, a sum of 1112 subjects approved to the intensive care unit were evaluated with a retrospective

study conducted by Chen et al., and the uric acid values of these patients at the time of admission were collected. The relationship between ICU and 90-day mortality and plasma uric acid values of patients were examined. No difference was reported between uric acid level and mortality, as in our study [4]. In addition to this study, in a prospective study by Aminiahidashti et al., 120 subjects received to the intensive care unit in 2014 were examined, and no significant relationship was detected between the uric acid level of the patients and intensive care mortality whereas the high uric acid level prolonged the span of mechanical ventilation [10].

In a prospective research conducted in the United States of America in 2015, the relationship between plasma uric acid values and intensive care mortality of patients received to the intensive care unit due to sepsis was reviewed, and it was concluded that the intensive care mortality increased as the uric acid value increased [3].

In a study conducted by Yeter et al, the relationship between uric acid/albumin proportion and mortality in intensive care patients was examined. The authors found a strong correlation between hypoalbuminemia and early mortality. They determined the cut-off value for albumin as 2.86. They observed that mortality increased at albumin values below 2.86. They asserted that the uric acid/albumin ratio was a valuable biomarker in predicting acute kidney injury, and it was a valuable biomarker in predicting intensive care mortality [11]. Our study consequences are in full compatibility with the study results of Yeter et al. The study of Yeter et al. is the first study in the literature searching the relationship between uric/acid albumin ratio and mortality. Our research is the second study in the literature. There are no other studies researching the relationship between acid/albumin ratio and mortality.

Guler et al. examined the relationship of albumin and hemoglobin values with hospitalization time and mortality in geriatric patients operated for thigh fractures. They discovered that there was no relationship between albumin and hemoglobin values and mortality [12]. In our study, we observed that mortality increased as albumin values decreased. Meanwhile, as our albumin values decreased, our APACHE-II and SOFA scores, which were our intensive care mortality scores, increased. The relationship between hypoalbuminemia and intensive care mortality was proven many times in our study with different analysis methods.

Likewise, in pediatric intensive care units and mortality studies, a significant relationship was detected between the low albumin level and mortality, and it was found out that albumin had a predictive value on mortality [13,14]. Even though our study was carried out with adult intensive care patients, our results fully coincide with the literature.

Msaad et al. investigated the factors causing mortality in hemodialysis patients. In their study, the researchers reported that albumin and prealbumin were the indicators of malnutrition and mortality in 126 hemodialysis patients. They expressed that mortality increased as the albumin and preaalbumin levels decreased [15]. Our study populations are different; however, our results are similar. Msaad et al. researched the albumin relationship in end-stage chronic kidney patients. In our study, that is to say, the relationship among hypoalbuminemia and deadness was investigated in critically care subjects with acute kidney injury.

Uric acid/creatinine ratio obtained when correction is made by proportioning to creatinine to neutralize the effect of possible serum uric acid level changes resulting from kidney functions is more sensitive than the uric acid level to show anaerobic changes caused by hypoxia. There are various studies indicating that the uric acid/creatinine is increased in cardiovascular and pulmonary and neuropsychiatric diseases which cause hypoxemia, such as chronic obstructive pulmonary disease, heart failure, cyanotic heart disease, pulmonary thromboembolism and pulmonary hypertension [16-18]. In our study, however, it was attributed that the uric acid/creatinine proportion was not correlated with deadness. Besides, the uric acid/creatinine proportion was detected to be lower in patients with acute kidney injury and patients who passed out. From this aspect the uric acid/creatinine ratio, our results are not compatible with the literature. The patient groups studied in the literature and our patient groups are quite different. Our difference from the literature in terms of the uric acid/creatine ratio may be related to the fact that our patient group is a completely different group.

Our research has some limitations. The retrospective style of the study is the first limiting factor. Moreover, examining the 90-day mortality of patients after drainage from the critically care service would have been useful in investigating the long-term effects of serum uric acid, uric acid/albumin and albumin levels.

Conclusion

Consequently, the uric acid/albumin ratio is a simple, inexpensive, useful biomarker which can be calculated practically. As albumin is a marker of mortality, the uric acid/albumin ratio can also be utilised as an identifier of mortality in intensive care patients. The uric acid/albumin ratio may be a useful biomarker in predicting prognosis in cases of acute kidney injury. We believe that our study will shed light on future studies on the uric acid/albumin ratio in larger populations and different patient groups.

Financial support and sponsorship: There are no financial support and sponsorship.

Conflict of interest: There are no conflicts of interest.

Ethical considerations: The study has obtained the approval of the ethical board with the ethical board decision number 10.10.2019/139 from Ordu University Clinical Research Ethics Committee.

Author contribution: Surgical and Medical Practices: E.Ç., Concept: E.Ç., M.Ş.A., Design: E.Ç., M.Ş.A., Y.E.G., Data Collection or Processing: E.Ç., M.Ş.A., Y.E.G., Ş.İ., Analysis or Interpretation: E.Ç., M.Ş.A., Y.E.G., Literature Search: E.Ç., M.Ş.A., Ş.İ., Writing: E.Ç.

References:

1. Aminiahidashti H, Bozorgi F, Mousavi SJ, Sedighi O, Gorji AM, Rashidian H. Serum Uric Acid Level in Relation to Severity of the Disease and Mortality of Critically Ill Patients. *J Lab Physicians*. 2017;9(1):42-46.

2. Lee HW, Choi SM, Lee J, et al. Serum Uric Acid Level as a Prognostic Marker in Patients With Acute Respiratory Distress Syndrome. *J Intensive Care Med.* 2019 ;34(5):404-410.

3. Akbar SR, Long DM, Hussain K, et al. Hyperuricemia: An Early Marker for Severity of Illness in Sepsis. *Int J Nephrol.* 2015;2015:301021.

4. Chen Q, Huang K, Li L, et al. Serum uric acid on admission cannot predict long-term outcome of critically ill patients: a retrospective cohort study. *Ther Clin Risk Manag.* 2018;14:1347-1359.

5. Pesquera JIM, Rubio AH, Ruiz IG, et al. La hiperuricemiacomo factor de riesgo cardiovascular y renal. *Diálisis y Trasplante*. 2011;32(2):57-61.

6. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. *Arthritis Rheum.* 2008;58(2):623-630.

7. Dawson J, Jeemon P, Hetherington L, et al. Serum uric acid level, longitudinal blood pressure, renal function, and long-term mortality in treated hypertensive patients. *Hypertension.* 2013;62(1):105-111.

8. Andrassy KM. Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. *Kidney Int.* 2013;84(3):622-623.

9. KDIGO Clinical Practice Guideline for Acute Kidney Injury. AKI definition. *Kidney International Supplements* 2012;2(1):19-22.

10. Aminiahidashti H, Bozorgi F, Mousavi SJ, Sedighi O, Gorji AM, Rashidian H. Serum Uric Acid Level in Relation to Severity of the Disease and Mortality of Critically Ill Patients. *J Lab Physicians.* 2017;9(1):42-46.

11. Yeter HH, Eyupoglu D, Pasayev T, Cetik S, Akçay OF, Yıldırım T. Role of Uric Acid Albumin Ratio in Predicting Development of Acute Kidney Injury and Mortality in Intensive Care Unit Patients. *Turk J Nephrol.* 2019; 28(3): 160-167.

12. Guler A, Dogukan M, Kaya R, Uludag O, Duran M, Tutak A. Retrospective Evaluation of the Effects of Albumin and Hemoglobin Values on the Duration of Hospital Stay and Mortality in Elderly Patients Operated for Hip Fracture. *ADYU Journal of Health Sciences.* 2018; 4(1):637-647.

13. Horowitz IN, Tai K. Hypoalbuminemia in critically ill children. *Arch Pediatr Adolesc Med*. 2007;161(11):1048-1052

14. Leite HP, Rodrigues da Silva AV, de Oliveira Iglesias SB, Koch Nogueira PC. Serum albumin is an independent predictor of clinical outcomes in critically ill children. *Critic Care Med.* 2016;17(2):e50-e57

15. Msaad R, Essadik R, Mohtadi K, et al. Predictors of mortality in hemodialysis patients. *Pan Afr Med J.* 2019; 33:61.

16. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. *Lung.* 2007;185(1):21-24.

17. Zhong LL, Song YQ, Tian XY, Can H, Ju KJ. Level of uric acid and uric acid/creatinine ratios in correlation with stage of Parkinson disease. *Medicine [Baltimore]*. 2018;97(26):e10967.

18. Albay VB, Tutuncu M. Are Uric Acid Level and Uric Acid/Creatinine Ratio Reliable Biomarkers for Idiopathic Parkinson's Disease Severity? *Med Bull Haseki.* 2020;58:315- 319.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Evaluation of prognosis and factors influencing the need for second look in patients with acute mesenteric ischemia

Rozan KAYA[1]
Abdulhakim İbrahim ULUSOY[2]
Ufuk Oguz IDİZ[3]

1. *İstanbul Eğitim ve Araştırma Hastanesi*
2. *Avcılar Murat Kölük Devlet Hastanesi*
3. *İstanbul Eğitim ve Araştırma Hastanesi*

Received: 7 January 2024
Accepted: 21 January 2024
Published: 31 January 2024

Corresponding Author: Rozan Kaya, ORCID ID: 0000-0002-5136-5873

Istanbul Training and Research Hospital, Department of General Surgery, Istanbul, Turkey

E-mail: rozankaya@hotmail.com

Abstract

Introduction: Acute mesenteric ischemia(AMI), a condition associated with high mortality risk and challenging diagnosis, typically arises due to arterial blockages in mesenteric vessels. Despite the absence of a specific diagnostic test for this condition, various markers are utilized in its diagnosis. In our study, we aimed to assess the clinical and laboratory results of patients requiring surgical intervention due to AMI.

Materials and Methods: Our study included 25 patients diagnosed with AMI between January 2017-January 2019. Demographic characteristics, comorbidities, time of hospital admission, blood parameters (leukocyte count, platelet count, amylase, lactate, arterial blood pH, bicarbonate, actate dehydrogenase), preoperative abdominal computed tomography results, duration of surgery, clinical course, need for secondary surgery within 48 hours postoperatively, additional resection requirement, and postoperative clinical follow-ups were recorded from hospital records.

Results: The mean age of patients was 70.2±12.7 years, with a male-to-female ratio of 14/11. Eighteen patients(72%) were identified to have occlusion in the superior mesenteric artery due to thrombosis or embolism. In seven of these patients(68%), secondary surgery was required within 48 hours postoperatively, with an additional resection needed in 12 cases. The group with a fatal outcome exhibited significantly higher lactate values compared to the surviving group. Among survivors, there was a trend indicating a shorter time from emergency room admission to surgery, but no statistically significant difference was observed. In patients requiring secondary surgery, leukocyte values post the initial surgery were observed to be higher, although not significantly, compared to those not requiring additional resection.

Conclusion: In elderly individuals with accompanying illnesses presenting to the emergency room with abdominal pain, the possibility of AMI should be considered. Elevated leukocyte and lactate levels may support the clinician's suspicion of AMI. Additionally, high leukocyte values in the postoperative period could serve as an indicator that ischemia may have progressed, necessitating secondary intervention.

Keywords: Mesenteric ischemia, leukocyte, second look, lactate

You may cite this article as: Rozan K, Abdulhakim İbrahim U, Ufuk Oguz I. Evaluation of prognosis and factors influencing the need for second look in patients with acute mesenteric ischemia. *Cerasus J Med*. 2024; 1(1):52-58.

Introduction

Acute mesenteric ischemia (AMI) is a critical emergency condition with a high risk of mortality and morbidity due to intestinal ischemia and infarction. Mortality rates can be as high as 65%, with delays in diagnosis and treatment being significant contributors to this outcome [1-3].

The main causes of mesenteric ischemia include mesenteric artery embolism (50% of cases), mesenteric artery thrombosis (15-25%), mesenteric venous thrombosis (5%), and non-occlusive mesenteric ischemia (20-30%) [4,5]. While open surgery is the primary treatment method, percutaneous transluminal angioplasty (PTA) and stenting are also utilized in endovascular treatment, offering faster blood flow and reducing the risk of mortality and morbidity [6-10].

Diagnosing mesenteric ischemia can be challenging, as severe abdominal pain may not always align with physical examination findings. Intravenous contrast-enhanced computed tomography (CT) is commonly preferred for diagnosis due to its high sensitivity and specificity, despite some guidelines recommending angiography as the gold standard [11,12,13,14].

Despite efforts, a specific biochemical marker for mesenteric ischemia diagnosis has not been established. While L-lactate, D-dimer levels, serum alpha-glutathione S-transferase, and nesfatin-1 have been reported to assist in diagnosis, a conclusive marker is yet to be determined [11,15].

The study aims to assess the impact of laboratory results and clinical findings on the diagnosis and prognosis of patients with acute mesenteric ischemia.

Materials and Methods

This retrospective study, conducted with ethical approval, involved reviewing the records of 1679 patients who presented to the emergency department with abdominal pain complaints and were referred to the General Surgery clinic between January 2017 and January 2019. Among them, 29 patients were diagnosed with acute mesenteric ischemia. Excluding four patients with incomplete information and those referred to different hospitals post-surgery, the study analyzed data from hospital records, including demographic details, comorbidities, admission time, blood parameters (leukocyte count, platelet count, amylase, lactate, pH, HCO3, and lactate dehydrogenase), surgery duration, secondary care needs at 48 hours postoperatively, additional resection requirements, and postoperative clinical follow-ups.

Patients were grouped based on postoperative survival and the need for additional resection during secondary surgery, with data comparisons between these subgroups. The study utilized the SPSS 20 program for variable analysis, assessing data distribution with the Kolmogorov-Smirnov test. Quantitative independent variables were analyzed using the independent sample t-test and Mann-Whitney U test, while the Wilcoxon test was applied for dependent quantitative variables. The Chi-square test was employed for qualitative independent variables analysis, and in cases where its conditions were not met, the Fisher's exact test was preferred.

Results

The study included 25 patients with a male-to-female ratio of 14/11 and an average age of 70.2±12.7 years. Only one patient (4%) had no comorbidities. Thrombosis or embolism in the superior mesenteric artery (SMA) was the cause of AMI in 72% of cases. Among the 17 patients, 68% underwent secondary surgery after 48 hours, with 12 requiring additional resection due to progressing intestinal ischemia. Demographic and clinical data are summarized in Table 1.

In examining the impact of collected data on mortality, a significant difference in lactate values (p:0.043) was noted between the group with mortality and the group without (Table 2). Surviving patients generally underwent surgery within 12 hours of emergency room admission, though this difference was not statistically significant. No significant variations were observed in other variables.

When patients undergoing secondary care were categorized based on the need for additional resection, no significant differences were found among the examined parameters. However, patients requiring additional resection exhibited significantly higher postoperative leukocyte values and significantly lower platelet values after the initial surgery (Table 3).

Parameter		
Age (year) (Mean±SD)	70.20±13.05	
Time Between Applying to the Emergency Department and Surgery (n,%)	<12 hour	11 (%44)
	≥12 hour	14 (%56)
Preoperative leukocyte x10³ (Mean±SD)		17.02±8.51
Postoperative leukocyte x10³ (Mean±SD)		17.27±10.74
Platelet x10³ (Mean±SD)		239.04±133.72
Arterial pH (Mean±SD)		7.31±0.09
Amilase (U/L) (Mean±SD)		126.08±103.54
Lactate (mmol/L) (Mean±SD)		3.42±1.68
Bicarbonate (HCO3) (mEq/L) (Mean±SD)		20.46±3.33
Lactate Dehydrogenase (U/L) (Mean±SD)		367.60±143.15

Table 1: Distribution of demographic and laboratory data of all patients

Parameter		Survival (n:8)	Exitus (n:17)	P value
Age (year) (Mean±SD)		68.63±14.84	70.94±12.55	0.662
Gender (n,%)	Female	4 (%50)	10 (%58.8)	1.000
	Male	4 (%50)	7 (%41.2)	
Time Between Applying to the Emergency Department and Surgery (n,%)	<12 hour	6 (%75)	8 (%47.1)	0.189
	≥12 hour	2 (%25)	9 (%52.9)	
Second Look (n,%)	No	3 (%37.5)	5 (%29.4)	1.000
	Yes	5 (%62.5)	12 (%70.6)	
Preoperative leukocyte x10³ (Mean±SD)		17.66±10.83	16.72±7.56	0.804
Postoperative leukocyte x10³ (Mean±SD)		15.53±12.06	18.08±10.35	0.591
Platelet x10³ (Mean±SD)		270.25±132.09	224.35±135.91	0.435
Arterial pH (Mean±SD)		7.35±0.09	7.29±0.08	0.152
Amilase (U/L) (Mean±SD)		148.38±126.36	115.59±93.43	0.727
Lactate (mmol/L) (Mean±SD)		2.46±1.41	3.88±1.63	0.043
Bicarbonate (HCO3) (mEq/L) (Mean±SD)		21.67±4.36	19.90±2.70	0.221
Lactate Dehydrogenase (U/L) (Mean±SD)		337.50±118.99	381.76±154.52	0.483

Table 2: Comparison of demographic and clinical data of patients who survived and those who died in the postoperative period

Parameter		No additional resection (n:5)	Additional resection required (n:12)	P value
Age (year) (Mean±SD)		71.60±11.52	68.25±13.88	0.712
Gender (n,%)	Female	3 (%60)	8 (%66.7)	1.000
	Male	2 (%40)	4 (%33.3)	
Time Between Applying to the Emergency Department and Surgery (n,%)	<12 hour	2 (%40)	8 (%66.7)	0.593
	≥12 hour	3 (%60)	4 (%33.3)	
Preoperative leukocyte x10^3 (Mean±SD)		15.30±4.63	18.44±10.54	0.537
Postoperative leukocyte x10^3 (Mean±SD)		13.80±7.52	20.90±12.51	0.175
Platelet x10^3 (Mean±SD)		315.40±129.77	211.00±108.73	0.108
Arterial pH (Mean±SD)		7.34±0.12	7.32±0.96	0.782
Amilase (U/L) (Mean±SD)		168.60±102.96	112.83±121.065	0.399
Lactate (mmol/L) (Mean±SD)		3.45±1.70	3.41±1.29	0.961
Bicarbonate (HCO3) (mEq/L) (Mean±SD)		21.88±5.24	20.23±3.41	0.673
Lactate Dehydrogenase (U/L) (Mean±SD)		337.20±124.79	368.83±184.55	0.928

Table 3: Comparison of demographic and clinical data of patients who required and did not require additional resection during second look

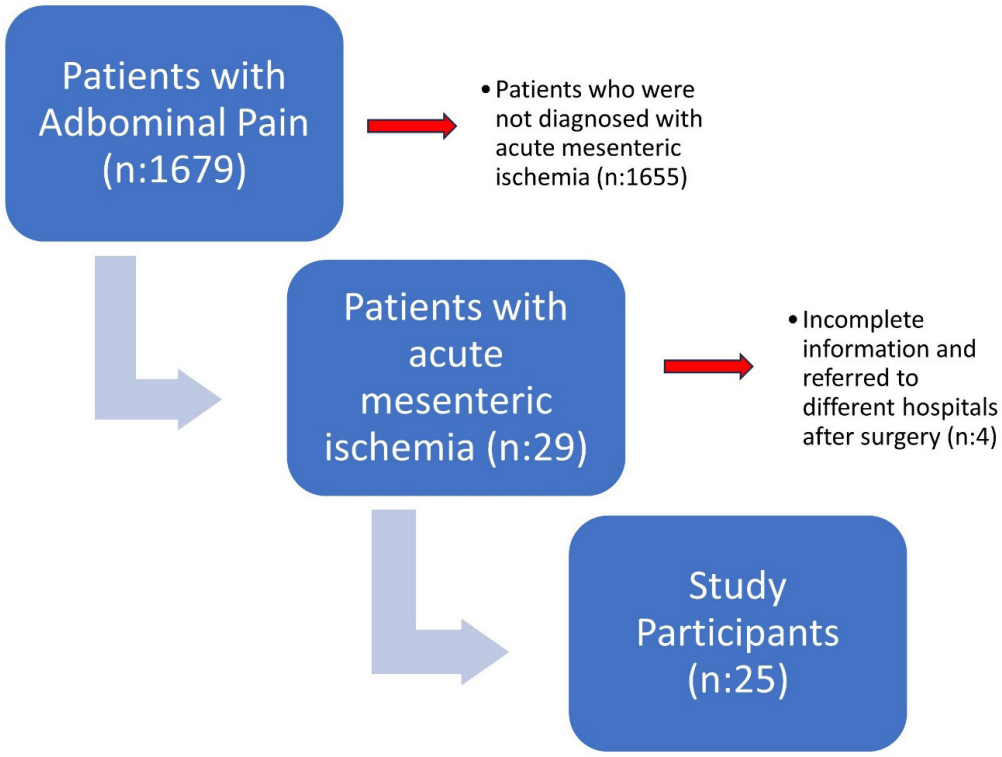


Figure 1: The flow diagram of study participants

Discussion

In 70-80% of AMI cases, ischemia occurs in the intestines due to mesenteric artery occlusion by an embolus or thrombus. Compared to other causes of acute mesenteric ischemia, embolic occlusion leads to early ischemia and transmural necrosis due to the absence of advanced collateral circulation [16]. Severe abdominal pain is a prominent symptom in AMI diagnosis, although it may be disproportionate to physical findings. Intestinal ischemia typically manifests before the onset of peritonitis and sepsis symptoms [17]. The intestines can tolerate a 75% reduction in blood flow for up to 12 hours, thanks to collaterals providing vasodilation and increased oxygen levels [19]. Prolonged ischemia, however, can lead to vasoconstriction in blocked vessels, resulting in increased pressure and decreased collateral blood flow [4,20]. Our study indicates lower postoperative mortality in patients diagnosed and operated on within 12 hours from emergency room admission, underscoring the impact of early diagnosis on mortality.

Acute mesenteric ischemia is frequently observed in elderly individuals, with some studies suggesting that increasing age is a poor prognostic sign for mesenteric ischemia. However, certain publications assert no relationship between age and AMI prognosis [17]. In our study, there was no significant age difference between surviving and deceased patients during the postoperative period.

Arterial emboli and thromboses typically result in obstructions in the superior mesenteric artery (SMA), while venous thromboses occur in the superior and inferior mesenteric veins, splenic veins, and portal veins [18]. Our study noted that in most patients, acute mesenteric ischemia (AMI) was caused by emboli or thromboses in the SMA.

Although the American College of Gastroenterology guidelines designate angiography as the gold standard for mesenteric ischemia diagnosis, non-invasive techniques like CT angiography are preferred due to their 96% sensitivity and 94% specificity, considering the invasiveness, limited accessibility, and time-consuming nature of angiography [11, 13, 14]. In our study, angiography was not performed due to its invasiveness and accessibility challenges; instead, an arterial CT angiography protocol was applied to the patients' CT scans.

Various laboratory tests have been explored for mesenteric ischemia or infarction diagnosis [25]. A review indicated that lactate levels provided 86% sensitivity and 44% specificity for AMI [26]. The specificity of elevated serum lactate levels significantly increases when conditions like shock, diabetic ketoacidosis, renal, and hepatic failure are excluded [27]. Approximately half of patients with intestinal ischemia have been observed to have elevated amylase levels, and about 80% have elevated phosphate levels [28-30]. Increased levels of blood urea, creatinine, and amylase, along with an increase in leukocyte count and changes in acidity, have been considered indicators of mortality in different studies [31, 32-36]. Although not statistically significant, some studies have reported that the development of leukopenia increases mortality and is associated with a decrease in the protective effect of the immune system [37]. In our study, among the examined blood parameters, only a significant increase in lactate levels was found in patients who experienced mortality during the postoperative period. Although no significant result was found among the parameters examined to determine the need for additional resection during secondary care, it is noteworthy that patients requiring additional resection had significantly higher postoperative leukocyte values and significantly lower platelet values.

The manuscript is limited by a small sample size, retrospective design, and a single-center focus, impacting the generalizability of the findings. Larger, diverse samples and prospective multi-center studies would enhance future research validity.

Conclusion

In summary, it is imperative to consider the potential occurrence of acute mesenteric ischemia (AMI) when assessing elderly individuals who present to the emergency room with abdominal pain and concurrent comorbidities. Vigilance and a high index of suspicion are crucial in managing these patients due to the absence of a definitive diagnostic test with both high sensitivity and specificity for mesenteric ischemia. Delays in diagnosis, exacerbated by the lack of a foolproof diagnostic tool, can contribute to increased

mortality rates. Clinicians should take note of elevated leukocyte and lactate levels, which can serve as valuable indicators supporting the suspicion of AMI. The absence of a rapid and precise diagnostic method underscores the importance of relying on clinical clues such as these for timely intervention. Moreover, monitoring leukocyte values in the postoperative period becomes instrumental, as persistently high levels may signal the progression of ischemia. Recognizing these markers and promptly addressing them is essential for optimizing patient outcomes and potentially averting the need for more extensive secondary care measures.

Funding

There is no institution or person supporting this study.

Conflict of Interest

None of the authors have a conflict of interest.

Authors' contribution: Surgical and Medical Practices: R.K., A.İ.U, U.O.İ, Concept: R.K., Design: R.K., A.İ.U, U.O.İ, Data Collection or Processing: R.K., A.İ.U, U.O.İ, Analysis or Interpretation: R.K., A.İ.U, U.O.İ, Literature Search: R.K., A.İ.U, U.O.İ, Writing: R.K., A.İ.U, U.O.İ

References

1. Stoney RJ, Cunningham CG. Acute mesenteric ischemia. *Surgery.* 1993;114(3):489-490.

2. Oldenburg WA, Lau LL, Rodenberg TJ, et al. Acute mesenteric ischemia: a clinical review. *Arch Intern Med.* 2004;164(10):1054-1062.

3. Cho JS, Carr JA, Jacobsen G, et.al. Long-term outcome after mesenteric artery reconstruction: a 37-year experience. *J Vasc Surg.* 2002;35(3):453-460.

4. Reinus JF, Brandt LJ, Boley SJ. Ischemic diseases of the bowel. *Gastroenterol Clin North Am.* 1990;19(2):319-343.

5. Zhao Y, Yin H, Yao C, et al. Management of Acute Mesenteric Ischemia: A Critical Review and Treatment Algorithm. *Vasc Endovascular Surg*. 2016;50(3):183-192.

6. Resch T, Lindh M, Dias N, et al. Endovascular recanalisation in occlusive mesenteric ischemia—feasibility and early results. *Eur J Vasc Endovasc Surg.* 2005;29(2):199-203.

7. Foley MI, Moneta GL, Abou-Zamzam AJ, et al. Revascularization of the superior mesenteric artery alone for treatment of intestinal ischemia. *J Vasc Surg.* 2000;32(1):37-47.

8. Schoots IG, Levi MM, Reekers JA, et al. Thrombolytic therapy for acute superior mesenteric artery occlusion. *J Vasc Interv Radiol.* 2005;16(3):317-329.

9. Sharafuddin MJ, Nicholson RM, Kresowik TF, et al. Endovascular recanalization of total occlusions of the mesenteric and celiac arteries. *J Vasc Surg.* 2012;55(6):1674-1681.

10. Cappell MS. Intestinal (mesenteric) vasculopathy. I. Acute superior mesenteric arteriopathy and venopathy. *Gastroenterol Clin North Am.* 1998;27(4):783-vi.

11. Tatar C, Ahlatci FA, Idiz UO, et al. May Nesfatin-1 be a Biomarker in Acute Mesenteric Ischemia? *J Coll Physicians Surg Pak.* 2019;29(10):928-931.

12. Copin P, Zins M, Nuzzo A, et al. Acute mesenteric ischemia: A critical role for the radiologist. *Diagn Interv Imaging*. 2018; 99(3):123-34.

13. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: initial experience. *Radiology.* 2003;229(1):91-98.

14. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. *Semin Vasc Surg.* 2010;23(1):9-20.

15. Bala M, Kashuk J, Moore EE, et al. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. *World J Emerg Surg.* 2017;12:38.

16. Hokama A, Kishimoto K, Ihama Y, et al. Endoscopic and radiographic features of gastrointestinal involvement in vasculitis. *World J Gastrointest Endosc.* 2012;4(3):50-56.

17. Yıldırım D, Hut A, Tatar C, et al. Prognostic factors in patients with acute mesenteric ischemia. *Turk J Surg.* 2017;33(2):104-109.

18. Bulkley GB, Kvietys PR, Parks DA, Perry MA, Granger DN. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. *Gastroenterology.* 1985;89(4):852-857.

19. Boley SJ, Frieber W, Winslow PR, et al. Circulatory responses to acute reduction of superior mesenteric arterial flow. *Physiologist.* 1969; 12:180.

20. McKinsey JF, Gewertz BL. Acute mesenteric ischemia. *Surg Clin North Am.* 1997;77(2):307-318.

21. Ofer A, Abadi S, Nitecki S, et al. Multidetector CT angiography in the evaluation of acute mesenteric ischemia. *Eur Radiol.* 2009;19(1):24-30.

22. Aschoff AJ, Stuber G, Becker BW, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. *Abdom Imaging.* 2009;34(3):345-357.

23. Kernagis LY, Levine MS, Jacobs JE. Pneumatosis intestinalis in patients with ischemia: correlation of CT findings with viability of the bowel. *AJR Am J Roentgenol.* 2003;180(3):733-736.

24. Taourel PG, Deneuville M, Pradel JA, Régent D, Bruel JM. Acute mesenteric ischemia: diagnosis with contrast-enhanced CT. *Radiology*. 1996;199(3):632-636.

25. Glenister KM, Corke CF. Infarcted intestine: a diagnostic void. *ANZ J Surg*. 2004;74(4):260-265.

26. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. *Acad Emerg Med*. 2013;20(11):1087-1100.

27. Lange H, Jäckel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. *Eur J Surg*. 1994;160(6-7):381-384.

28. Wilson C, Imrie CW. Amylase and gut infarction. *Br J Surg*. 1986;73(3):219-221.

29. Gearhart SL, Delaney CP, Senagore AJ, et al. Prospective assessment of the predictive value of alpha-glutathione S-transferase for intestinal ischemia. *Am Surg*. 2003;69(4):324-329.

30. Jamieson WG, Marchuk S, Rowsom J, Durand D. The early diagnosis of massive acute intestinal ischaemia. *Br J Surg*. 1982;69 Suppl:S52-S53.

31. Aliosmanoglu I, Gul M, Kapan M, et al. Risk factors effecting mortality in acute mesenteric ischemia and mortality rates: a single center experience. *Int Surg*. 2013;98(1):76-81.

32. Acosta-Merida MA, Marchena-Gomez J, Hemmersbach-Miller M, Roque-Castellano C, Hernandez-Romero JM. Identification of risk factors for perioperative mortality in acute mesenteric ischemia. *World J Surg*. 2006;30(8):1579-1585.

33. Acosta S, Wadman M, Syk I, Elmståhl S, Ekberg O. Epidemiology and prognostic factors in acute superior mesenteric artery occlusion. *J Gastrointest Surg*. 2010;14(4):628-635.

34. Graeber GM, Cafferty PJ, Reardon MJ, Curley CP, Ackerman NB, Harmon JW. Changes in serum total creatine phosphokinase (CPK) and its isoenzymes caused by experimental ligation of the superior mesenteric artery. *Ann Surg*. 1981;193(4):499-505.

35. Schwartz LB, Gewertz BL. Mesenteric ischemia. *Surg Clin North Am.* 1997; 77: 275-502.

36. Huang HH, Chang YC, Yen DH, et al. Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department. *J Chin Med Assoc*. 2005;68(7):299-306.

37. Mamode N, Pickford I, Leiberman P. Failure to improve outcome in acute mesenteric ischaemia: seven-year review. *Eur J Surg*. 1999;165(3):203-208

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Does the continuous intraarticular pain pump effective to decrease the pain after total knee arthroplasty?

Tuğcan DEMİR[1]
Fatma ALKAN BAYBURT[2]
Muhammet BOZOĞLAN[3]
Azime BULUT[2]
Kürşat AYTEKIN[1]

1. *Department of Orthopedics, Giresun University*
2. *Department of Anesthesiology and Reanimation, Giresun University*
3. *University of Health Sciences, İzmir Tepecik Health Research Center Department of Orthopedics*

Received: 9 January 2024
Accepted: 31 January 2024
Published: 31 January 2024

Corresponding Author: Tuğcan DEMİR, ORCID ID: 0000-0002-0273-832X

Department of Anesthesiology and Reanimation,Giresun University Faculty of Medicine, Giresun 28100, Turkey

E-mail: tugcandem@hotmail.com

Abstract

Objective: This study aims to show the efficiacy of continuous intraarticular pain pump administration after total knee arthroplasty for pain management.

Material and Methods: This retrospective study was conducted on bilateral knee arthroplasty surgery patients. The patients who has one-sided continuous intraarticular pain pump were investigated. The Visual analogue scale (VAS), at the 8th hour, 24th hour, 2nd weekend 1st month and the range of motion (ROM) at the 24th hour, 2nd weekend 1st month were evaluated at both knees.

Results: Twenty-six patients (25 female, 1 male) met the study criteria. The mean age was 71.66±5.07 years (63-81 years). The continuous intraarticular pain pump used knees were associated with a significant decrease in the VAS at the 8th and 24th hours. Though there were no differences in the range of motion between pain pump used and non-used knees at the 48th, 2nd weekend 1st month. No pain pump-related complications were detected.

Conclusion: Using a continuous intraarticular pain pump is effective in treating pain after total knee prosthesis. This benefit on pain relief does not make a significant difference in the range of motion of the knee.

Keywords: Total knee arthroplasty; pain pump; visual analogue scale; range of motion

You may cite this article as: Demir T, Bayburt Alkan F, Bozoğlan M, Bulut A, Aytekin K. Does the continuous intraarticular pain pump effective to decrease the pain after total knee arthroplasty?. *Cerasus J Med*. 2024; 1(1):59-64.

Introduction

Total knee arthroplasty (TKA) is the major treatment method for relieving pain in severe joint impairment but has a very painful erly post-operative period. High postoperative pain levels may cause patient dissatisfaction, decreased knee range of motion, increased narcotic analgesic use and prolonged hospital length of stay [1]. Besides, if severe postoperative pain is managed inadequately, the increased oxygen demand and higher strain on the cardiovascular system after a major operation such as TKA may pose serious damage to the patient [2].

Therefore, proper pain management after TKA is essential for the comfort of the patient, early functional recovery and to decrease the length of stay in the hospital. Multiple techniques have been used to provide pain control such as epidural analgesia, peripheral nerve block, periarticular injection and patient-controlled analgesia [3,4]. Continuous intraarticular local anesthetic infusion through elastomeric pumps is one of these techniques. Concern on chondrotoxic effects of local anesthetics in recent years have limited the use in arthroscopic surgeries but reports on their effectiveness after TKA are increasing in numbers. Mauerhanet al reported continuous intraarticular bupivacaine administration decreases pain but only four hours postoperatively [3]. Gomez–Cardero et al used ropivacaine and reported decreased pain, opioid use, and reduced hospital stay [4].

Our aims were to evaluate the effecivenesst of continuous intraarticular bupivacaine injection for postoperative pain control and to determine the effect of the pain pump on the recovery of postoperative range of motion of the knee.

Material and Methods

After ethics committee approval (19/09/2018, KAEK-57), patients who underwent bilateral total knee arthroplasty between January 2015 and July 2018 were screened retrospectively. The patients whose medical files were accessible, diagnosed with bilateral primary gonarthrosis, underwent bilateral total knee arthroplasty, operated under spinal anesthesia, had at least one month follow-up and applied a single knee continuous intraarticular pain pump were included to the study. Inflammatory diseases, diabetic neuropathy, psychiatric diseases, and allergies to morphine or local anesthetics medicines were the exclusion criteria for the study.

The biggest health insurance provider in our country only pays for one continuous intraarticular pain pump in one surgical session. All patients included in the study were informed in detail preoperatively about the function of the continuous intraarticular pain pump and also were informed that the pain pump could only be applied to one knee. An informed consent form was obtained from all the patients.

All the patients were operated as the first case in the morning and underwent spinal anesthesia. A tourniquet was placed on both lower extremities but not inflated. The tourniquet was inflated only at the cementation phase. Both lower extremities were stained with povidone-iodine. Firstly, surgery was performed on the left knee. The right lower extremities were re-stained and re-covered before beginning right knee surgery. All the patients underwent surgery with the same surgical team. All surgeries were done with a medial parapatellar approach. All patients had the same brand of prostheses (Smith & Nephew, Genesis II CR, USA). At the end of the surgery, the skin was closed with subcutaneous absorbable sutures and stapled.

Intraarticular drains were placed in both knees. The continuous intraarticular pain pump (ON-Q® PainBuster®, 270 mg, USA) was used only in one knee (left). The pain pump was prepared with 180 ml saline and 60 ml Marcaine® (AstraZeneca, Turkey, Kırklareli). The pain pump was inserted into the joint and was activated at the end of the operation with a 5 ml/hour infusion. The activation of the drain began in the second hour for 15 minutes and continued in this way every two hours. The standard protocol for painkillers was administered (Paracetamol 100 mg infusion 4X1 (Perfalgan®, Bristol-MyersSquibb, France), tramadol hydrochloride 100 mg 4X1 (Ultramex, ADEKA, Turkey), dexketoprofentrometamol 50 mg 1x1 (Arveles, Menarini, Turkey). In addition, 15 minutes of cold application was used every 2 hours. Subcutaneous enoxaparin 0.6 mL 1x1 (Clexane, Sanofi Aventis, Turkey) was applied for deep vein thrombosis prophylaxis for the first 10 days. For infection prophylaxis, cefazoline sodium 2x1 g (Cefamezine, Zentiva, Turkey) and gentamicin 80 mg (Genta, Bilim,

Turkey) were administered for two days. At the first postoperative day, all patients began active knee flexion with closed chain exercises for knee flexion and isometric quadriceps exercises with straight leg raise for knee extension. The patients were ambulated with double crutches. The pain pump and drains were removed at 48 hours. VAS values at the 8th and 48th hours, second weekend first month postoperatively were evaluated for each knee separately. The evaluations were made by the same orthopedic resident using the standard VAS pain scale. The loss of knee extension degree and flexion degree during knee closed chain were measured via a goniometer at 48th hours, second week and first month, postoperatively.

Statistical analysis

All data were analyzed using SPSS vn. 21.0 software (IBM Corpn., Armonk, NY, USA). Shapiro-wilk test was used to evaluate whether the data had a normal distribution or not. Two dependent variables with normal distribution were analyzed with the paired sample test and the wilcox on signed ranks test was used for two dependent variables that did not have a normal distribution. In all the comparisons, statistical significance was set at the level of $p<0.05$.

Results

The study consisted of 26 patients (25 female, 1 male) and the mean age was 71.66 ±5.07 years (63-81years).

The VAS scores of the patients at the 8th hour were 4.73±1.079 and 2±0.938 (right and left knee, respectively)(p=0.00). At the 48th hour, the VAS scores were 6.42±0.945 and 2.50±1.068 (right and left knee, respectively) (p=0.00). At the 2nd week the VAS scores for the right knee were 2.50±1.334 and the VAS scores for the left knee were 2.31±1.192 (p=0.096). At the 1st month, the VAS scores were 1.35±0.745 for the right knee and 1.27±0.667 for the left knee (p=0.414) (Table1).

The loss of knee extension degree of the patients at 48th hours were 16.38˚±4.801 and 13.88˚±4.752 (right and left knee, respectively) (p=0.57). These values were 9.38˚±3.817 for the right knees and 8.46˚±3.952 for the left knees at second week (p=0.404). At the 1st month, the loss of extension degrees of the right knees were 3.58˚±2.802 and the loss of extension degrees of the left knees were 2.88˚±2.123 (p=0.507) (Table2).

The knee flexion degrees of the patients at 48th hours were 68.42˚±10.458 and 72.69˚±10.781(right and left knee, respectively) (p=0.58). At the second week, the knee flexion degrees of the patients were 98.23˚±9.197 and 98.96˚±8.987 (right and left knee, respectively) (p=0.512). These values were 111.81˚±9.724 for the right knees and 113.58˚±9.257 for the left knees at the first month (p=0.411) (Table3).

There were not observed any skin complication, prolonged drainage, early enfection or systemic bupivacain side effect (eg, nausea, vomiting, dizziness) in the study group.

Discussion

This study highlights pain assessment of the patients in which a continuous intraarticular pain pump was used just for one knee after bilateral total knee arthroplasty surgery. The only difference between the knees that were evaluated in the study was whether or not to use a continuous intraarticular pain pump. VAS pain scores were found to be significantly lower in knees using a pain pump at the eight hand forty-eight hours.

Table 1: VAS pain scores at the follow-ups

VAS	Mean±Std Degrees		p
	R Knee	L Knee	
8th hours	4.73±1.079 (3-7)	2.00±0.938 (1-4)	0.000
48th hours	6.42±0.945 (5-8)	2.50±1.068 (1-5)	0.000
2ndweeks	2.50±1.334 (0-5)	2.31±1.192 (0-4)	0.096
1st month	1.35±0.745 (0-3)	1.27±0.667 (0-2)	0.414

R: Right, L: Left, p: Significance value, VAS: Visual Analogue Scale

Table 2: Loss of knee extension degreesat the follow-ups

ROM	Mean±Std Degrees		p
	R Knee	L Knee	
48th hours	16.38±4.801(7-30)	13.88±4.752 (5-25)	0.57
2nd weeks	9.38±0.817 (4-21)	8,46±3.952 (3-20)	0.404
1st month	3.58±2.802 (0-9)	2.88±2.123 (0-7)	0.507

R: Right, L: Left, p: Significance value, ROM: Range of Motion

Table 3: Knee flexion degrees at the follow-ups

ROM	Mean±Std Degrees		p
	R Knee	L Knee	
48th hours	68.42±10.458 (40-88)	72.69±10.781(45-90)	0.58
2nd weeks	98.23±9.197 (85-119)	98.96±8.987 (85-120)	0.512
1st month	111.81±9.724 (92-130)	113.58±9.257 (95-130)	0.411

R: Right, L: Left, Std: Standart deviation, p: Significance value, ROM: Range of Motion

Knee prosthesis surgery is an effective method to improve knee functions and pain due to arthrosis. After surgery, 60% of patients feel severe pain, while 30% of patients feel pronounced levels of pain [5]. There is no gold standard protocol for pain control, which effects postoperative rehabilitation and the duration of stay in the hospital. In the literature, generally opioid, NSAID and peripheral block use were described. Though these treatments were used, a variety of side effects were reported (nausea, vomiting, motor block and other GIS side effects) [6-9]. Continuous intraarticular analgesic administration aims to reduces systematic drug requirements and thus minimizing these side effects and simultaneously ensure better pain control. Williams et al. reported pain scores and morphine consumption did not reduce using a 0.5% bupivacaine infusion pump over 48 hours [10]. Ali et al. compared an infusion pump with a placebo in a study and did not identify pronounced clinical differences in VAS pain scores, hospital stay, morphine consumption and drug side effects. They reported they stopped clinical administration due to identifying an increase in deep infections [9]. Rasmussen et al. used morphine and ropivacaine infusion to reduce pain after knee prosthesis and ensured early mobilization and they reported hospital stay shortened, knee flexion increased and morphine consumption reduced in this way [11]. Ong et al. reported that patient-controlled intravenous morphine infusion with an additional bupivacaine infusion pump was effective in reducing pain, reducing morphine consumption and increasing function [12]. Goyal et al. identified a clear reduction in VAS scores and opioid requirements, especially in the first 2 days in a study comparing placebo with bupivacaine infusion. The same study did not observe any difference between the two groups in terms of complications [13]. In this study, we identified the VAS scores were better in the 8th and 48th hours for the knees with the infusion pump. We observed the analgesic requirements for knees without pumps were more pronounced, especially in the first 48 hours. We did not identify any significant difference in VAS scores in the 2nd weekend 1st month.

There are a variety of studies about the effects on ROM of local anesthetic administration after knee surgery. Mullaji et al. administered local infiltration (bupivacaine, fentanyl, methylprednisolone acetate, cefuroxime) to single knees in addition to the analgesic

treatment protocol in patients with TKA performed on both knees. During follow-up, they identified that VAS scores were low on the infiltration side during postoperative 1st day, discharge day, 2nd and 4th week check-ups. In the same study knee flexion was found significantly better on the infiltration side at discharge, 2nd weekend 4th week. Especially in 4th week controls, only 5 patients had flexion below 120 degrees on the infiltration side, while 16 patients without infiltration had flexion below 120 degrees [14]. Busch et al. compared knee prosthesis patients with local injection of ropivacaine, ketorolac, apomorphine and epinephrine mixture with patients without injection and did not find any significant differences in terms of knee ROM at 6-week check-up [15]. Gomez-Cardero et al [4] identified a significant fall in VAS score and opioid requirements for patients with ropivacaine intraarticular infusion compared to the placebo group and stated that there was higher knee ROM especially until the 1st month, with the same level of ROM after the first month. In this study, both the extension loss and flexion degress of the knees that continuous intraarticular pain pump used or not used did not show a significant difference. Although it is thought that postoperatively good pain relief will increase functional results, we found that pain level and functional recovery were not positively correlated in this patient group.

There is variety in the local infiltrative drugs and their administration durations. These drugs have a very similar half-life time. The half-life of bupivacaine is 3.5 hours, while ropivacaine varies from 2-6 hours [12]. In their meta-analysis, Zhang et al. did not directly compare these two drugs but reported that indirect comparisons found that ropivacaine had a more protective effect against pain. Additionally, 2 cc/hour infusions were reported to be more effective on 24-hour and 48-hour VAS scores compared to infusions below 2 cc/hour [16]. The Daily recommended bupivacaine limit is 400 mg [17]. In this study, we used 300 mg bupivacaine in a continuous infusion of 5 cc/hour. We did not observe any skin complications or systematic bupivacaine side effects. We obtained a clear benefit for VAS scores on eight and forty-eight hours.

The main limitation of this study is the small number of patients but with our knowledge in the literature, there is no study that assesses the effect of continuous intraarticular pain pump in the single knee on patients with bilateral total knee arthroplasty. All the other studies were designed with a placebo. The biggest advantage of this study is; the control group of the continuous intraarticular pain pump usage is the other knees of the same patients. Therefore, we think that the evaluation of the efficacy of the continuous intraarticular pain pump in this study provides more accurate results.

Conclusion: Pain management with a continuous intraarticular pump is an effective method for eight and forty-eight hours after total knee arthroplasty. This treatment does not provide beneficial effects for postoperative functional recovery.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author' Contributions: Concept: K.A., Design: K.A., Data Collection or Processing: F.A.B., M.B., A.B., Analysis or Interpretation: T.D., Literature Search: T.D., Writing: T.D., M.B.

References

1. Horlocker TT. Pain management in total joint arthroplasty:a historical review. *Orthopaedics* 2010;33(9):14-19.

2. Korean Knee Society. Guidelines for the management of postoperative pain after total knee arthroplasty. Knee Surg Relat Res. 2012;24(4):201-207.

3. Mauerjan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. *J Arthroplasty.* 1997;12(5):546-552.

4. Gómez-Cardero P, Rodríguez-Merchán EC. Postoperative analgesia in TKA: ropivacaine continuous intraarticular infusion. *Clin Orthop Relat Res*. 2010;468(5):1242-1247.

5. Bonica JJ. Postoperative pain. In: Bonica JJ (ed): The management of pain. (2nd ed). Philadelphia: Lea

and Febiger, 1990, pp. 461-480.

6. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA.* 2003;290(18):2455-2463.

7. Jakobsen TL, Kehlet H, Husted H, Petersen J, Bandholm T. Early progressive strength training to enhance recovery after fast-track total knee arthroplasty: a randomized controlled trial. *Arthritis Care Res (Hoboken).* 2014;66(12):1856-1866.

8. Pelt CE, Anderson AW, Anderson MB, Van Dine C, Peters CL. Postoperative falls after total knee arthroplasty in patients with a femoral nerve catheter: can we reduce the incidence?. *J Arthroplasty.* 2014;29(6):1154-1157.

9. Ali A, Sundberg M, Hansson U, Malmvik J, Flivik G. Doubtful effect of continuous intraarticular analgesia after total knee arthroplasty: a randomized double-blind study of 200 patients. *Acta Orthop*. 2015;86(3):373-377.

10. Williams D, Petruccelli D, Paul J, Piccirillo L, Winemaker M, de Beer J. Continuous infusion of bupivacaine following total knee arthroplasty: a randomized control trial pilot study. *J Arthroplasty.* 2013;28(3):479–484.

11. Rasmussen S, Kramhøft MU, Sperling KP, Pedersen JHL. Increased flexion and reduced hospital stay with continuous intraarticular morphine and ropivacaine after primary total knee replacement: open intervention study of efficacy and safety in 154 patients. *Acta Orthop Scand.* 2004;75(5):606-609.

12. Ong JC, Chin PL, Fook-Chong SM, Tang A, Yang KY, Tay BK. Continuous infiltration of local anesthetic following total knee arthroplasty. *J Orthop Surg (Hong Kong)*. 2010;18(2):203-207.

13. Goyal N, McKenzie J, Sharkey PF, Parvizi J, Hozack WJ, Austin MS. The 2012 Chitranjan Ranawat award: intraarticular analgesia after TKA reduces pain: a randomized, double-blinded, placebo-controlled, prospective study. *Clin Orthop Relat Res.* 2013;471(1):64-75.

14. Mullaji A, Kanna R, Shetty GM, Chavda V, Singh DP. Efficacy of periarticular injection of bupivacaine, fentanyl, and methylprednisolone in total knee arthroplasty: a prospective, randomized trial. *J Arthroplasty.* 2010;25(6):851-857.

15. Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *J Bone Joint Surg Am.* 2006;88(5):959-963.

16. Zhang Y, Lu M, Chang C. Local anesthetic infusion pump for pain management following total knee arthroplasty: a meta-analysis. *BMC Musculoskelet Disord.* 2017;18(1):32. Published 2017 Jan 23.

17. Abbot Laboratories. Bupivacaine hydrochloride injection and epinephrine injection package inserts. North Chicago, IL: Abbot Laboratories, 1998.

CERASUS JOURNAL OF MEDICINE

Aortic infection accompanied by Leriche syndrome: Presenting with acute mesenteric ischemia and spleen abscesses

Uluhan ERYURUK[1]
Tümay BEKCİ[1]
Serdar ASLAN[1]

1. *Giresun University, Faculty of Medicine, Department of Radiology, Giresun, Turkey*

Received: 8 January 2024
Accepted: 25 January 2024
Published: 31 January 2024

Corresponding Author: Uluhan Eryuruk, ORCID ID: 0000-0001-6581-621X
Giresun University, Faculty of Medicine, Department of Radiology, Giresun, Turkey
E-mail: uluhaneryuruk@gmail.com

Abstract

Aortoiliac occlusive disease, also referred to as Leriche syndrome, is an obstruction of the distal abdominal aorta, iliac and femoropopliteal arteries by cause of atherosclerotic process. The coexistence of aortoiliac occlusive disease and aortic infection has been mentioned in hardly any cases in the literature. Air presence in the aorta is not uncommon in inflammatory and infective conditions. However, aortic air without pseudoaneurysm formation has rarely been reported and is important in the early diagnosis of aortic infections. This report describes a patient with aortic infection accompanied by Leriche syndrome, causing acute mesenteric ischemia and spleen abscesses.

Keywords: Leriche syndrome, Mesenteric ischemia, Spleen abscess, Aortic infection

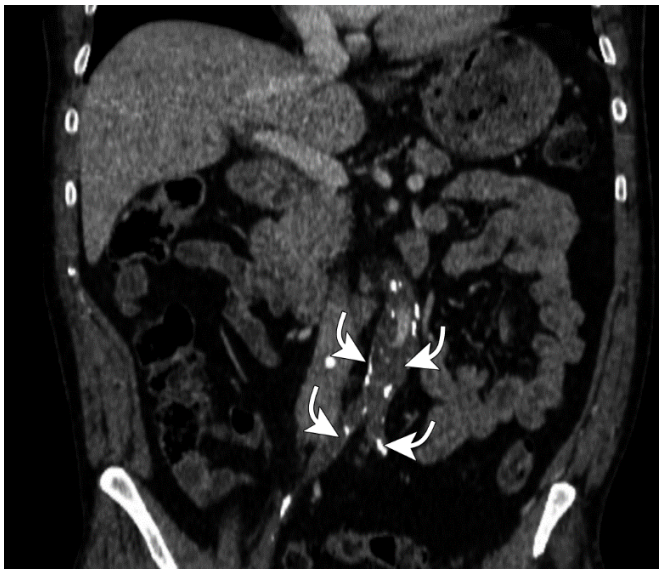
A 78-year-old male patient with known aortoiliac occlusive disease (**Figure 1**) was admitted to our emergency department (ED) complaining of fever and abdominal pain. On physical examination, the patient had a fever of 39 °C and generalized abdominal tenderness. His blood pressure was 90/50 mm Hg, and his heart rate was 95 beats per minute. Laboratory investigations revealed renal failure, with a creatinine level of 4.5 mg/dL and a urea level of 205 mg/dL. The white blood cell count was 10,750 cells/mm^3, and the C-reactive protein (CRP) level was 386 mg/L.

Contrast-enhanced imaging was not performed because of the renal

You may cite this article as: Eryuruk U, Bekci T, Aslan S. Aortic infection accompanied by Leriche syndrome: Presenting with acute mesenteric ischemia and spleen abscesses. *Cerasus J Med*. 2024; 1(1):65-67.

failure. Unenhanced abdominal computed tomography (CT) revealed air bubbles in the thrombotic aortic lumen at the infrarenal level **(Figure 2A)**. In addition, intestinal ischemia findings, such as portal venous gas and pneumatosis intestinalis, and multiple spleen abscesses were observed **(Figure 2B-C)**. Based on these laboratory and imaging findings, acute mesenteric ischemia and splenic abscesses caused by septic embolism due to aortic infection were considered. Therefore, emergency surgery or systemic anticoagulant treatment was not administered. After broad-spectrum antibiotic treatment started in the ED, clinical improvement was observed in the patient's renal functions and bowel ischemia findings.

Figure

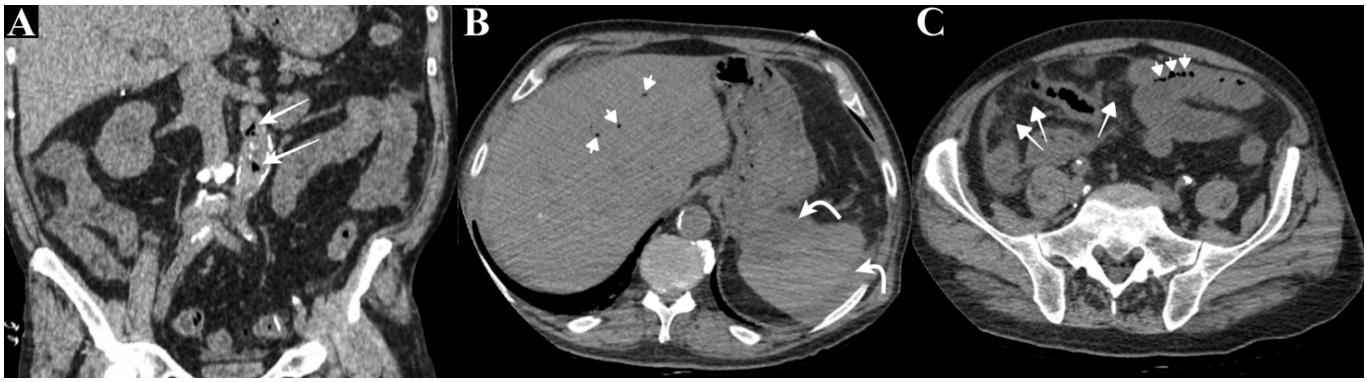


1. Contrast-enhanced CT performed four months before the patient's admission to the emergency department (ED), showing total occlusion of the infrarenal aorta and bilateral iliac arteries (curved arrows).

Aortoiliac occlusive disease, also known as Leriche syndrome, is an atherosclerotic disease characterized by complete occlusion of the abdominal aorta and both iliac arteries. The absence of femoral pulses, erectile dysfunction, and claudication in the pelvis and thighs are among the findings of the disease. An infection of aortoiliac thrombosis is extremely rare and has been reported in only a few cases in the literature [1-3]

Acute mesenteric ischemia due to septic embolism is a very specific scenario. It has been reported in only a few cases of infective endocarditis and, its treatment is enigmatic. The main therapeutic dilemma is related to the use of anticoagulation, and there is insufficient data on its use in the literature [4]. In our case, anticoagulant treatment was not initiated in the ED or during follow-up.

Gas presence in the aorta is not uncommon in inflammatory and infectious processes. However, air bubbles without pseudoaneurysm formation have rarely been reported and are important in the early diagnosis of aortic infections [1]. Mycotic aortic aneurysm accompanied by Leriche syndrome has been reported in the literature, albeit in few cases. In these reports, both surgical treatment and antibiotic therapy alone were used as treatment modalities [1-2]. In our case, the diagnosis was made by the presence of air in the thrombotic aortic lumen without the formation of a pseudoaneurysm, and clinical improvement was achieved with an antibiotherapy.



2.A. Coronal view of non-enhanced abdominal CT performed on admission to the ED, showing the presence of gas (arrows) in the occluded aortic lumen at the infrarenal level.**B.** Axial unenhanced abdominal CT images showing peripherally located portal venous gas (short arrows) and spleen abscesses (curved arrows).**C.** Axial view of unenhanced abdominal CT showing findings of acute mesenteric ischemia findings: presence of pneumatosis intestinalis (short arrows) and mesenteric stranding (long arrows).

To our knowledge, this is a unique presentation of infected aortoiliac thrombosis, which has not yet been reported in the literature. In the ED, infected aortic thrombosis and its complications should be considered in patients with Leriche syndrome, especially in the presence of aortic air on non-contrast abdominal CT. Being aware of this unusual scenario will be helpful in initiating appropriate treatment in the ED and correct management of the patient.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Authors' Contributions: Concept: S.A., T.B. Design: U.E. LiteratureSearch: S.A., T.B., U.E. Writing: T.B., U.E.

References

1. Yang CY, Liu KL, Lee CW, Tsang YM, Chen SJ. Mycotic aortic aneurysm presenting initially as an aortic intramural air pocket. *AJR Am J Roentgenol*. 2005;185(2):463-465.

2. Furui M, Hirata H, Kakii B et al. Successful Surgical Treatment of an Infected Thoracoabdominal Aneurysm Accompanied with Leriche Syndrome. *Case Rep Surg*. 2019;2019:1628157. doi:10.1155/2019/1628157.

3. Norikane T, Yamamoto Y, Takami Y, Tani R, Nishiyama Y. Infectious Aortic Aneurysm in a Patient With Leriche Syndrome. *Clin Nucl Med*. 2022;47(12):e740-e741.

4. Waqas M, Waheed S, Haider Z, Shariff AH. Acute mesenteric ischaemia with infective endocarditis: is there a role for anticoagulation? *BMJ Case Rep*. 2013:bcr2013009741. doi:10.1136/bcr-2013-009741.

CERASUS JOURNAL OF MEDICINE

CASE REPORT

Is it really rheumatoid arthritis?

Evren ER[1]

1. *Tokat Erbaa Devlet Hastanesi*

Received: 3 January 2024
Accepted: 13 January 2024
Published: 31 January 2024

Corresponding Author: Tuğcan DEMİR, ORCID ID: 0000-0003-2456-9106

Tokat Erbaa Devlet Hastanesi

E-mail: ewrener@hotmail.com

Abstract

Rheumatoid arthritis; it is an autoimmune disease that usually shows symmetrical polyarticular involvement and positivity for rheumatoid factor and anti-cyclic citrullated peptide can be observed. Patients may not have antibody positivity, but rheumatoid arthritis may be present and these patients are defined as seronegative rheumatoid arthritis. It is expected decrease acute phase reactants levels and disease activity scores of patients who start treatment. It is important to review the diagnosis, especially in patients with seronegative rheumatoid arthritis who do not respond to treatment. In this case report, a patient who was followed up with the diagnosis of seronegative rheumatoid arthritis and was diagnosed with soft tissue tumor in his hand is presented.

Keywords: Physical and Rehabilitation Medicine, Rheumatoid Arthritis, Soft Tissue Neoplasms

You may cite this article as: Er E. Is it really rheumatoid arthritis?. C*erasus J Med*. 2024; 1(1):68-71.

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting approximately 1% of the world's population [1]. It is usually characterized by symmetrical polyarticular involvement, morning stiffness, and inflammatory pain [2]. Rheumatoid factor (RF) and anti-cyclic citrullated peptide (Anti-CCP) positivity are frequently observed in patients [3]. Both RF and anti-CCP negativity is thought to be 10-48% among RA patients and these patients are defined as seronegative RA [4]. In the differential diagnosis, osteoarthritis, other rheumatic diseases with polyarticular involvement, and infectious factors such as hepatitis B virus and chikungunya virus that cause polyarthritis should be considered [5,6]. It is necessary to review the diagnosis, especially in seronegative RA patients who do not respond to treatment. In this case report, a patient who was followed up with the diagnosis of seronegative RA and was diagnosed with soft tissue tumor in his hand is presented.

Case Presentation

A 42-year-old female patient says that she has been followed up with the diagnosis of RA for about 5 years. Therefore, she said that she used methotrexate 10 mg/week subcutan, hydroxychloroquine 400 mg/day, prednisolone 5 mg/day, folic acid 5 mg/week. She applied to us because she was not benefiting from the medications, the swelling in her hand was gradually increasing, and she had bruising on her fingers. There was discoloration on the palmar surface of the 4th and 5th fingers of the right hand, diffuse swelling localized at the proximal and middle phalangeal levels, there was no temperature increase, and the range of motion of the finger joints was slightly limited (Figure 1).

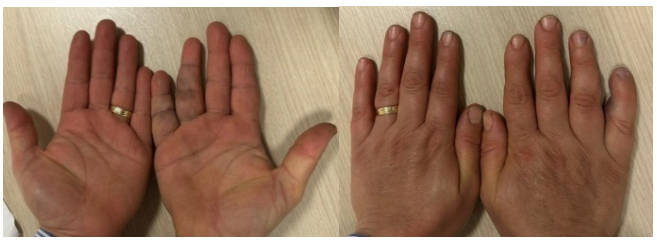


Figure 1. Image of hands and fingers

In laboratory examination, c reactive protein (CRP) was 1.72 mg/L, erythrocyte sedimentation rate (ESR) was 20 mm/h, and no pathological findings were observed in complete blood count (CBC), kidney and liver function tests. RF and anti-CCP autoantibodies were negative. In anteroposterior hand radiographs imaging, soft tissue swellings were observed in the 4th and 5th fingers of the right hand (Figure 2). Disease activity score 28 (DAS28) score was calculated as 2,43. There was no evidence of synovitis in ultrasonography (USG). In contrast-enhanced right hand magnetic resonance imaging (MRI), multiple tubular space-occupying lesions were observed in the soft tissue of the 4th and 5th fingers (Figure 2). The patient's medications were stopped and the patient was referred to hand surgery.

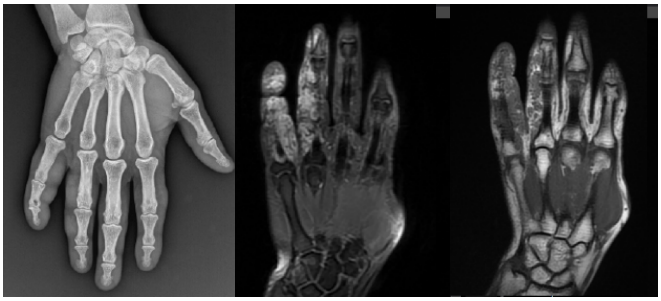


Figure 2. Right hand finger anteroposterior hand radiographs and MRI

Discussion

Swelling, synovitis, and pain in the joints may be observed in RA attacks [2]. In the presence of disease activity, an increase in the level of acute phase reactants and deterioration in CBC parameters are expected [3]. RF and anti-CCP positivity are frequently observed in patients [3]. Erosions can be observed in joints on X-ray imaging [7]. Ultrasonographic examinations during an attack help in diagnosis and can detect the presence of arthritis, synovitis and joint erosion [8]. There are American College of Rheumatology 2010 (ACR2010) classification criteria for RA [9]. According to these criteria, a score of 6 or above supports the diagnosis of RA. Synthetic disease-modifying anti-rheumatic drug (DMARD), biological DMARD and target-sensitive DMARD options are available in treatment [10,11]. Simple disease activity index (SDAI), clinical disease activity index (CDAI) and DAS28 are used to evaluate disease activity and treatment response [12,13].

It is expected that the symptoms will regress and the joint swelling will decrease with treatment. In addition to clinical response, improvement in acute phase reactants levels and CBC parameters is expected

in patients who benefit from treatment. If there is a response in treated patients, it supports the diagnosis. DAS28, CDAI and SDAI scores are expected to decrease in treated patients [12]. Patients may be primary or secondary unresponsive to treatment [11]. Other treatment options may be considered in patients who do not respond to treatment.

In our case, joint involvement was asymmetrical, there was swelling only in the 4th and 5th fingers, and swelling was unrelated to attacks. Contrary to what was expected in RA, there was neither synovitis nor erosion on USG. In addition; findings such as unresponsiveness to treatment, normal acute phase levels, RF and anti-CCP negativity, absence of erosion on x-ray do not match the findings of RA. Patient's ACR2010 score was less than 6. Although there was no treatment response, the DAS28 score was low. Considering the patient's findings, it is thought that symptoms are thought to result from an etiology other than RA. Therefore additional imaging was performed. A soft tissue tumor was detected in the patient's hand during additional imaging. Soft tissue masses in the hand are rarely observed and can be detected through imaging methods in undiagnosed patients [14].

As a result, although RF and anti-CCP positivity is expected in RA patients, concept of seronegative RA causes diagnostic confusion in antibody-negative patients. It is necessary to review the diagnosis and ensure that other diagnoses are excluded, especially in seronegative RA patients who do not respond to treatment.

Conflicts of interest: The author declare there is no conflicts of interest.

Funding: None.

Author' Contributions: Concept: E.E., Design: E.E., Data Collection or Processing: E.E., Analysis or Interpretation: E.E., Literature Search: E.E., Writing: E.E.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016; 388(10055):2023-2038. doi:10.1016/S0140-6736(16)30173-8.

2. Akiyama M, Kaneko Y. Pathogenesis, clinical features, and treatment strategy for rheumatoid arthritis-associated interstitial lung disease. *Autoimmun Rev*. 2022;21(5):103056. doi: 10.1016/j.autrev.2022.103056.

3. Rönnelid J, Turesson C, Kastbom A. Autoantibodies in Rheumatoid Arthritis - Laboratory and Clinical Perspectives. *Front Immunol.* 2021;12:685312 doi: 10.3389/fimmu.2021.685312.

4. Pratt AG, Isaacs JD. Seronegative rheumatoid arthritis: pathogenetic and therapeutic aspects. *Best Pract Res Clin Rheumatol.* 2014;28(4):651-659. doi: 10.1016/j.berh.2014.10.016.

5. Villa-Blanco JI, Calvo-Alén J. Elderly onset rheumatoid arthritis: differential diagnosis and choice of first-line and subsequent therapy. *Drugs Aging.* 2009;26(9):739-750. doi: 10.2165/11316740-000000000-00000.

6. Kumar R, Ahmed S, Parray HA, Das S. Chikungunya and arthritis: An overview. *Travel Med Infect Dis.* 2021;44:102168. doi: 10.1016/j.tmaid.2021.102168.

7. Lerch K, Herold T, Borisch N, Grifka J. Die Bildgebung beim rheumatischen Ellenbogen [Imaging in rheumatoid arthritis of the elbow]. *Orthopade.* 2003;32(8):691-698. doi: 10.1007/s00132-003-0509-z.

8. Sakellariou G, Montecucco C. Ultrasonography in rheumatoid arthritis. *Clin Exp Rheumatol.* 2014;32:20-25.

9. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology (Oxford).* 2012;51:5-9. doi: 10.1093/rheumatology/kes279.

10. Radu AF, Bungau SG. Management of Rheumatoid Arthritis: An Overview. *Cells.* 2021;10(11):2857. doi: 10.3390/cells10112857.

11. Ataman Ş, Sunar İ, Yilmaz G, et al. Turkish League Against Rheumatism (TLAR) Recommendations for the Pharmacological Management of Rheumatoid Arthritis: 2018 Update Under Guidance of Current Recommendations. *Arch Rheumatol.* 2018;33(3):251-271. doi: 10.5606/ArchRheumatol.2018.6911.

12. Pu LM, Liu Y, Zhou DX, et al. Development

and validation of equations for conversion from DAS28ESR and DAS28CRP to the SDAI in patients with rheumatoid arthritis. *Clin Rheumatol.* 2022;41(12):3697-3706. doi: 10.1007/s10067-022-06259-z.

13. Smolen JS, Aletaha D. Scores for all seasons: SDAI and CDAI. *Clin Exp Rheumatol.* 2014;32(5):75-79.

14. Stacy GS, Bonham J, Chang A, Thomas S. Soft-Tissue Tumors of the Hand-Imaging Features. *Can Assoc Radiol J.* 2020;71(2):161-173. doi: 10.1177/0846537119888356.