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Editorial

In issue 4 (3) of Aurum Journal of Health Sciences, three original research articles and one review are published. These articles are "Brown/Beige Adipose Tıssue: Novel Players In The Fight Against Obesity", "Classification of COVID-19 Omicron Variant Using Hybrid Deep Transfer Learning Based on X-Ray Chest Images", "Explanation of Mortality Rates With Socio-Economic Indicators" and "Health 4.0 and Health 4.0 Technology Applications".

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Prof. Dr. Osman Nuri Uçan
Editor-in-Chief, Aurum Journal of Health Sciences

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RESEARCH ARTICLE

BROWN/BEIGE ADIPOSE TISSUE: NOVEL PLAYERS IN THE FIGHT AGAINST OBESITY

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Abstract

Obesity is a metabolic disease which its prevalence is increasing worldwide. Multidisciplinary strategies are required to combat obesity. Many methods, from diet to surgery, are tried in obesity treatment. However, these methods have not been successful enough in the treatment of obesity. In recent years, a new adipose tissue type has been mentioned, with very important developments in adipose tissue biology. This type of adipose tissue is named as beige adipose tissue, different from white adipose tissue and classical brown adipose tissue. It has been observed that the beige adipocytes have a Brown-like characteristic and have thermogenesis abilities. It has been shown that beige adipocytes can develop in the white adipose tissue by a mechanism called browning, with the effect of various stimuli such as cold, hormones, exercise and dietary compounds. Brown/beige adipocytes are a candidate to be a new generation weight loss strategy and it is likely to have benefits against both obesity and its related metabolic diseases such as insulin resistance, diabetes, etc. To date, an increasing number of studies have been carried out to combat obesity by inducing browning of WAT by trying many compounds or methods, including cold exposure, various drugs, hormones, and plant-based agents. With the use of new generation nanotechnology-based therapies in the near future, specific molecules that can directly bind to brown/beige fat cells and activate the thermogenic program will be able to treat obesity. However, the therapeutic use of browning agents in people with obesity in the coming years will depend on the outcome of further randomised controlled trials.

Keywords: Obesity, Brown adipose tissue, Beige Adipose Tissue, Browning of white adipose tissue

1. INTRODUCTION

Obesity is a metabolic disease that threatens public health caused by both genetic factors and environmental, psychological and social factors, and its prevalence is increasing worldwide. Currently, it is reported that 2.2 billion people worldwide are overweight and 712 million people are obese (Cheng et al., 2021). A healthy adult person's body mass index (BMI) should be below 25 kg/m2. However, in diseases such as obesity, BMI in humans rises above 30 kg/m^2. Obesity occurs when energy intake exceeds energy expenditure (Pan et al., 2020).

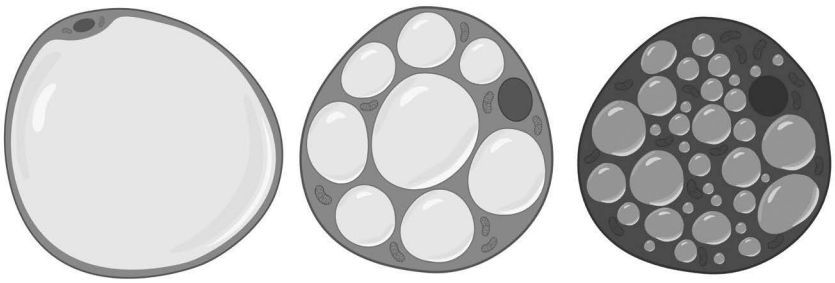
Multidisciplinary strategies are needed to combat obesity. Many methods, from diet and weight loss programs to endoscopic or bariatric surgery, are tried in the treatment of obesity. (Yoneshiro et al., 2013). However, these methods are unsuccessful in some obese patients. Therefore, it is of great importance to develop alternative methods for the fight against obesity. In recent years it has been recognized that brown/beige adipocytes have enormous metabolic benefits: Only 63 g of brown/beige adipocytes can burn about 4 kg of WAT per year (Cypess et al., 2013; Virtanen et al., 2009). Many studies have shown that activation of brown/beige adipogenesis can contribute to energy expenditure, suppressing obesity. To date, an increasing number of studies have been carried out to combat obesity by inducing WAT browning by trying many compounds or methods, including cold exposure, various drugs, hormones, and plant-based agents (Wankhade et al 2016; Herz and Kiefer, 2019). In this review, we will summarize subjects including adipose tissue types and characteristics of especially beige/brown adipose tissue. In addition, we will discuss in detail WAT browning, which is a current approach in the treatment of obesity, and the agents used for this purpose. Finally, we will consider nanotechnology-based drug delivery approaches in the treatment of obesity.

2. ADIPOSE TISSUE

In recent years, with increasing research, it has been revealed that adipose tissue is not only a tissue where energy is stored, but also a tissue with many functional roles for metabolism, which plays a fundamental role in food intake, energy homeostasis, insulin sensitivity, blood pressure and angiogenesis with various hormones and adipokines secreted from adipocytes. It has been shown to be a very important tissue and consequently an endocrine organ (Halberg et al., 2008). There is a large amount of adipose tissue around the subcutaneous, abdominal cavity, skeletal muscle, mammary glands and vessels of a normal adult (Berry et al., 2013). Adipose tissue acts as a fuel tank for metabolism and contributes to most of the vital needs of the organism. It also has crucial roles in thermogenesis, hormone synthesis and release, lactation and immune response (Cinti, 2012; Harms and Seale, 2013).

Traditionally, two types of adipose tissue are mentioned. First, white adipose tissue (WAT) is responsible for storing excess energy as triacylglycerol (TAG) and releasing free fatty acids (FFA) for energy when needed, while the second type is brown adipose tissue (BAT), which mainly performs thermogenesis

function (Berry et al., 2013). However, a third new class of adipose tissue has been mentioned in recent years. These adipocytes, on the other hand, were named beige adipocytes as a new and separate cell type different from white and brown adipocytes (Wu et al., 2012; Harms and Seale, 2013). The main characteristics of white, brown and beige adipocytes are shown in Figure 1.



	White Adipocyte	Beige Adipocyte	Brown Adipocyte
Function	Storage of triglycerides, endocrine (secretion of adipokines and vasoactive factors)	Thermogenesis, anti-inflammatory properties, cardioprotective	Thermogenesis, anti-inflammatory properties, cardioprotective
Depots	Visceral and subsutaneous and most PVAT depots	Cervical*, supraclavicular*, axillary*, renal*, thoracic PVAT*, paraspinal* subcutaneous (only rodents)	Interscapular (human only infants) thoracic PVAT*
Lipid Droplet	Uni-locular	Multi-locular	Multi-locular
UCP-1 Expression	-	+	+++
Mitochondrial Density	Low	Medium	High
Progenitor	PDGFRα^{+}, CD24^{+}, CD34^{+}	Vascular smooth muscle origin	Myogenic origin En-1, Myf5^{+}, Pax7^{+}
Changes during obesity	Hyperplasia, hypertrophy, secretion of vasoconstrictors, immune cell infiltration	Whitening, loss of UCP-1 expression	Potentially resistant to obesity-induced inflammation

Figure 1. The characteristics of white, brown and beige adipocytes

2.1. White Adipose Tissue

WAT is generally found all over the body and is classified as visceral (vWAT) and subcutaneous (sWAT) depots according to its location. Following excessive food intake or low energy expenditure, WAT can take both FFA and glucose from blood plasma and convert them to triglycerides. However, in humans, re-esterification of fatty acids is more preferable than de novo lipogenesis from glucose (Virtue et al., 2012). WAT is dominated by a single large vacuole that stores triglycerides, but still shows vascularity. WAT is also highly innervated with both afferent and efferent sympathetic nerves (Bartness and Song, 2007; Bartness et al., 2014; Merlin et al., 2016). WAT can regulate nutritional status by secreting inflammatory mediators, including adipokines such as leptin, adiponectin, resistin, and tumor necrosis factor-α (TNF-α) into the vascular and lymphatic systems. Considered in the context of obesity, these mediators play a central role both locally by affecting adipocyte proliferation and differentiation, and by controlling satiety and energy catabolism (Galic et al., 2010; Ouchi et al., 2011). On the other hand, in the case of obesity, hyperplasia, hypertrophy, secretion of vasoconstrictors, and immune cell infiltration are observed in the white adipose tissue.

2.2. Brown Adipose Tissue

BAT functions by consuming energy rather than energy storage and generating heat when activated. This process is known as non-shivering thermogenesis (Cypess et al., 2009). The most well-known role of BAT for a long time is that it plays an important role in protecting animals from hypothermia, mostly in hibernating animals. Furthermore, BAT is a rapidly activating tissue to maintain body temperature at birth in both humans and rodents and therefore functions in neonates. However, it is known that BAT in humans decreases with age. (Harms and Seale, 2013). But recent studies have shown that BAT exists in adults as well. (Nedergaard et al., 2007). In recent years, significant amounts of brown/beige adipocytes have been found in adult humans, especially in supraclavicular, cervical, paravertebral, perirenal, and mediastinal regions, as a result of the contributions of an in-depth examination of adipose tissue with 18F-fluorodeoxyglucose Positron Emission Tomography combined with Computed Tomography (18F-FDG-PET/CT). In humans, BAT depots are found to be much less than WAT. Moreover, it has been reported that BAT depots decrease with age (Bartelt and Heeren, 2014).

BAT is also called multilocular adipose tissue. BAT has many blood capillaries and contains a lot of mitochondria. It shows dense nervous networks. Macroscopically, the tissue appears brown due to the presence of heme cofactors in the mitochondrial enzyme cytochrome oxidase. BAT has a more limited distribution than WAT, which is found throughout the body. Compared to WAT cells, BAT cells are small and polygonal. It contains large amounts of lipid droplets of various sizes in its cytoplasm. It also has a centrally located nucleus and abundant long cristae mitochondria (Cedikova et al., 2016).

Low ATP synthase activity is shown in mitochondria found in brown adipocytes, Therefore, mitochondria cannot use the proton gradient to produce ATP. Instead, they use uncoupling protein-1 (UCP-1), which

uncouples cellular respiration and ATP synthesis, thereby releasing heat instead of ATP (Kajimura and Saito. 2014). Knock-out UCP-1 mice have been reported to be obese. (Feldmann et al., 2009).

2.3. Beige Adipose Tissue

Recent studies have shown that fat cells expressing UCP-1 can develop in WAT in response to various stimuli (cold, thyroid hormone, some hormones, various drugs, nutrients, etc.). These adipocytes, on the other hand, were named "beige" (Brite, brown-white, brown-like, induced brown) adipocytes as a distinct group from WAT and BAT (Harms and Seale, 2013; Wu et al., 2012). The reason why it is named this way is because beige adipocytes; Unlike myocytes and "classic" brown adipocytes, it do not originate from myogenous factor 5 (MYF5)-positive adipomyoblasts, but from MYF5-negative mesodermal stem cells such as white adipocytes (Merlin et al., 2016).

Principally, the idea that targeting brown/beige adipose tissue can be a therapeutic strategy to combat obesity is prominent. Brown and beige adipocytes in humans were found more than a decade ago with 18F-FDG-PET/CT imaging. (Nedergaard et al., 2007; Cypess et al., 2009; Virtanen et al., 2009). The presence of beige adipocytes in humans has been demonstrated by anatomical and transcriptomic methods in addition to 18F-FDG-PET/CT imaging. As a result of all these findings, it was revealed that beige adipocytes are mainly located in the supraclavicular regions (Jespersen et al., 2013), while the cervical region consists of classical brown adipocytes (Cypess et al., 2013). In recent years, WAT browning has been imaged using Mitochondrial Complex-I Tracer (^{18}F-BCPP-EF) (Goggi et al., 2022). With increasing evidence, it has been demonstrated that active human adipose tissues are heterogeneous. Although the deeper cervical adipose tissue in humans is similar in many respects to classical BAT in rodents, it has been shown that adipose tissue in the supraclavicular region of humans has a mixture of brown and beige adipocytes (Cypess et al., 2013; Shinoda et al., 2015; Jespersen et al., 2013).

Beige adipocytes were infiltrated in WAT. They contain more dense mitochondria than white adipocytes but less dense than brown adipocytes. Like BAT, beige adipocytes consist of multilocular lipid droplets and show high vascularization and sympathetic nervous system (SNS) innervation and expression of thermogenic genes such as UCP-1, peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), PPARα, and cell death-inducing DFFA Like Effector A (CIDEA) (Ahmad et al., 2021; Harms and Seale, 2013; Wang and Seale, 2016; Wankhade et al., 2016). Beige adipocytes are similar in structure to white adipocytes under normal conditions. But they have the ability to increase heat production and energy expenditure under certain stimuli (β-adrenergic stimulation, diet or exposure to cold). This makes it similar in function to brown adipocytes. However, after the stimulus is withdrawn, beige adipocytes begin to change their expression profile and morphological structure and display white adipocyte features again (Altshuler-Keylin et al., 2016). Aging, obesity, and overall poor metabolic responses are associated with loss of BAT ("whitening") and reduced capacity to induce browning (Harms and Seale, 2013). Findings from cell lineage studies in mice show that beige adipocytes develop

directly from white adipocytes and smooth muscle cells after exposure to cold. (Lee et al., 2014; Long et al., 2014). In humans, beige adipocytes, which are the intermediate form of adipose tissue, are found in both subcutaneous and visceral regions (Saito, 2014).
Studies on mice have shown that beige adipocytes play an important role in the clearance of lipids from plasma and the treatment of hyperlipidemia (Bartelt et al., 2011). Beige adipose tissue also has effects on glucose tolerance (Guerra et al., 2001). It is predicted that the conversion of WAT to beige adipocytes may be a promising target in the treatment of obesity and related complications such as insulin resistance, type 2 diabetes, hypertension, and cardiovascular diseases (Tan et al., 2011).

2.4. Lineage of White, Brown and Beige Adipocytes

Figure 2 demonstrates the lineage of white and brown beige adipocytes. Adipogenic, myogenic, or osteogenic cells arise from common mesenchymal stem cells (MSCs). White adipocytes are formed from MSCs from the adipogenic lineage (Myf 5^-) (Ahmad et al., 2021). It appears that white adipocytes are derived from mural progenitor cells expressing CD24, CD34 and PDGFRα (platelet-derived growth factor receptor alpha), and subcutaneous and visceral white adipocytes originate from different progenitor populations (Rodeheffer et al., 2008; Berry and Rodeheffer, 2013; Gesta et al., 2006). There are many factors in determining the adipogenic lineage of stem cells such as bone morphogenetic proteins (BMPs), transforming growth factor β (TGF-β), fibroblast growth factor 1 and 2 (FGF 1 and 2), insulin-like growth factor 1 (IGF1), activin, interleukin 17 (IL-17), etc. Generally, white adipocytes are believed to arise from $Myf5^-$ progenitor cells. However, by showing that white adipocytes can also develop from $Myf5^+$ progenitor cells, it has been argued that the developmental origin of white adipocytes has a very complex character. Despite all this complexity, the notion that white adipocytes develop mainly from $Myf5^-$ progenitor cells is more dominant. (Sanchez-Gurmaches et al., 2012).

Because BAT protects the newborn against cold, its development and differentiation occur before birth (Park et al., 2014). In mice, classical brown adipocytes begin to express Pax7, Engrailed-1 (En-1), and Myf5 around days 9.5 to 11.5 of embryonic development. BAT originates from $Myf5^+$ progenitor cells (Koenen et al., 2021). These progenitor cells are cells that have the potential to differentiate into either myocytes or brown preadipocytes which then develop into mature brown adipocytes (Becerril et al., 2013; Ahmad et al., 2021). This process is influenced by BMP-7 (Tseng et al., 2008), PR domain containing 16 (PRDM16) (Harms et al., 2014), and early beta-cell factor 2 (EBF2) (Wang et al., 2014).

With the induction of these markers, an increase is observed in the expression of BAT-specific markers including Peroxisome proliferator-activated receptor gamma (PPARγ), PPARγ Coactivator-1α (PGC-1α) PR domain containing 16 (PRDM16), CCAAT enhancer-binding proteins (C/EBPs) etc. As a result of this increase in the expression of BAT-specific markers, the development of progenitor cells into brown preadipocytes is induced (Ahmad et al., 2021).

Unlike BAT, beige adipocytes develop in a different developmental way. Studies have revealed that beige adipocytes are formed from Myf5- progenitor cells or by trans differentiation of white adipocytes (Rui, 2017; Ikeda et al., 2018). They also have the characteristics of white adipocytes (Herz and Kiefer, 2019). Although beige and white adipocytes come from the same common origin, beige adipocytes appear to have a different transcriptional profile and metabolic role than those white adipocytes (Wang et al., 2015). Both brown and beige adipocytes also highly express PGC-1α, a key regulator of energy metabolism. Homeobox c9 (Hoxc9) is expressed in WAT and mouse beige adipocytes of subcutaneous adipose tissue origin. Lower expression is observed in human supraclavicular samples (Merlin et al., 2016). Previously, cell surface markers T-box transcription factor 1 (TBX1), transmembrane protein 26 (TMEM26) and CD137 were thought to be specific for beige adipocytes (Wu et al., 2012). However, as a result of recent studies, it has been questioned whether CD137 and TBX1 are suitable markers for beige adipocytes (Srivastava et al., 2020; Markan et al., 2020).

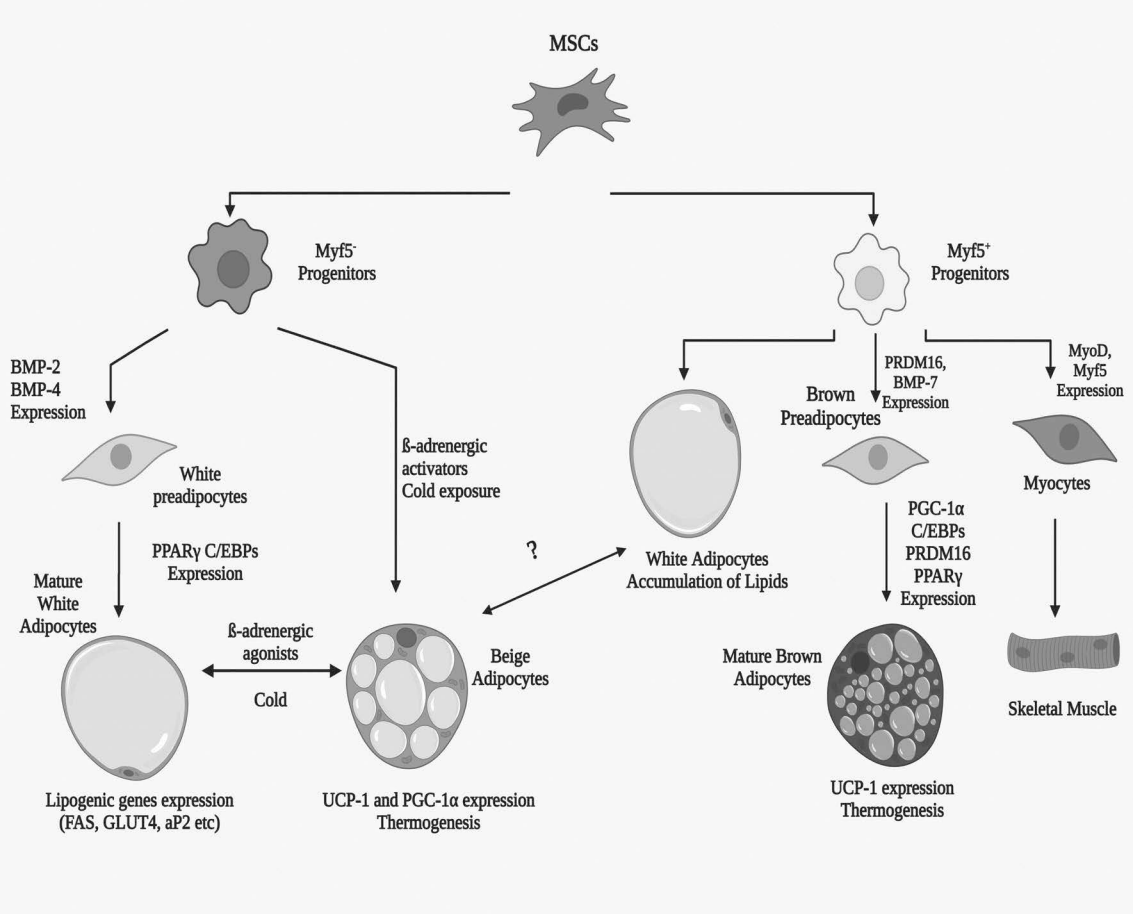


Figure 2. The lineage of white, brown and beige adipocytes

Interestingly, Chen et al. (2019) discovered a different form of thermogenic cell, which they called the glycolytic beige adipocytes. They reported that these cells showed thermogenesis and energy homeostasis even without β-AR signaling in cold conditions. The developmental origins, regulation and enhanced glucose oxidation of glycolytic beige adipocytes have been demonstrated showed to be different compared to conventional beige adipocytes.

2.5. Functions of Brown/Beige Adipose Cells

While the main function of WAT in our body is to store the excess energy as TAG, brown and beige adipocytes are a type of adipose tissue that is metabolically highly active to generate heat through their thermogenesis abilities and contribute to energy expenditure by using chemical energy. Brown/beige adipocytes are known to play a critical role mainly in thermogenesis, energy homeostasis, body temperature and body mass control. In addition to all these functions mentioned above, recent findings have revealed that BAT and beige adipocytes are undeniably involved in their metabolic function. Therefore, the possibilities of using them as possible therapeutic target cells against metabolic diseases are gaining importance (Wankhade et al., 2016).

The process of converting chemical energy into heat is called thermogenesis. Thermogenesis, which utilizes rapid muscle tremors to produce heat, is called shivering thermogenesis, while the type of thermogenesis created by BAT, a special tissue type that produces heat, is called non-shivering or adaptive thermogenesis (Azhar et al., 2016). The mitochondrial respiratory chain establishes a proton gradient for ATP production across the inner mitochondrial membrane. However, the UCP-1 protein, which is specific for brown/beige adipocytes, causes proton leakage from the inner membrane, preventing ATP generation through the phosphorylation of ADP after the mitochondrial respiratory chain and instead provides heat production (Chouchani et al., 2019). As a result, UCP-1 expression in BAT disrupts the electrochemical gradient that drives ATP synthesis in mitochondria and heat energy is released instead of ATP synthesis (Cinti, 2012). Although this process, called thermogenesis, is controlled by sympathetic stimulation of the β3-adrenergic receptor, fatty acids and thyroid hormones also play an important role in the necessary regulation (Harms and Seale, 2013).

The main receptor involved in the thermogenesis program is the Beta-3 adrenergic receptor (β-3 AR). The release of catecholamines such as norepinephrine as a result of sympathetic stimulation by cold exposure leads to mitochondria activation in brown/beige adipocytes. This provides more heat generation. Mechanistically, following cold exposure, the sympathetic nervous system releases norepinephrine. Norepinephrine binds to β3-AR, resulting in an increase in cAMP levels via activation of adenylyl cyclase and subsequently increased activation of protein kinase A (PKA) (Cypess et al., 2015). By activating this signal, p38 mitogen-activated protein kinase (p38 MAPK) stimulates transcription factor 2 (ATF-2), thereby activating the transcription of PGC1-α (Robidoux et al., 2005). PGC1- has significant downstream effects inducing mitochondrial biogenesis and PPAR activation (Hondares et al., 2011). One of the most important

effects of PGC1-α is that it activates nuclear respiration factor 1 (NRF1), whose nucleus communicates with mitochondria and triggers mitochondrial replication with the activation of mitochondrial transcription factor A (TFAM) (Piantadosi and Suliman, 2006). Consequently, the binding of norepinephrine to β3-AR triggers the signal that causes the release of FFA from brown/beige adipocytes, which is the main energy source for UCP-1-induced thermogenesis (Saito, 2014). In fact, reducing body mass through thermogenesis is not a novel concept and it should be noted that it still needs careful consideration for safety. For example, 2, 4-dinitrophenol (DNP), a mitochondrial uncoupling agent, has been shown to be effective for weight loss, but hyperthermia and other serious problems have been seen as side effects in patients treated with 2, 4-dinitrophenol (Grundlingh et al., 2011).

As a result of the balance between energy intake and energy expenditure, body mass is kept at a relatively constant level (Rui, 2013). It is further understood by experimental evidence that contributing to energy expenditure by activating thermogenesis through BAT activation or browning of WAT will be protective against obesity. In line with this concept, it has been shown that various nutrients, metabolites and some metabolic hormones can induce brown/beige adipogenesis. (Seale et al., 2009; Wankhade et al., 2016; Herz and Kiefer, 2019). BAT and beige adipocytes mediate diet-induced thermogenesis, at least in part. Thus, it prevents weight gain (Feldmann et al., 2009). Conversely, ablation of brown/beige fat has been observed to result in severe obesity in mice (Lowell et al., 1993). More importantly, chronic cold exposure has been reported to activate brown/beige adipocytes, thereby reducing body mass and fat mass in adult humans (Yoneshiro et al., 2013).

It is not surprising that brown/beige adipocytes have regulatory functions on metabolic homeostasis, given their critical role in the control of energy expenditure and regulation of body mass. Brown/beige adipocytes primarily use fatty acids for thermogenesis. In addition, BAT and beige fat may regulate glucose and lipid metabolism by a mechanism independent of body mass. Human brown and beige adipose cells are likely to similarly regulate glucose/lipid metabolism (Rui, 2017). It has been shown that keeping overweight/obese men in the cold for 5-8 hours (19.9 ± 0.8°C) activates BAT and increases gene expression related to lipid metabolism. (Chondronikola et al., 2016). Furthermore, it was observed that glucose uptake, glucose oxidation and insulin sensitivity increased in BAT of individuals exposed to cold for 10 days. (Chondronikola et al., 2014). BAT transplantation had positive effects on hyperglycemia and glucose intolerance in treptozotocin-induced or type 1 diabetes mice. (Gunawardana and Piston, 2012; Gunawardana and Piston, 2015). Insulin resistance was also reduced with BAT transplantation in high-fat diet (HFD)-induced obese recipient mice (Srivastava et al., 2012). In humans, body mass index, resting plasma glucose and lipid levels appear to be inversely related to BAT/beige fat mass (Saito et al., 2009). However, the mechanistic relationship between BAT/beige adipose tissue and insulin sensitivity and glucose metabolism has not been fully elucidated. In rodents, brown/beige adipocytes express and secrete abundant lipoprotein lipase (LPL) with cold exposure. Brown/beige adipocytes appear to play a critical role in maintaining blood TAG homeostasis in rodents (Bartelt et al., 2011).

It has been understood that WAT secretes many hormones and mediator molecules (adipokine) such as leptin and adiponectin, thereby helping to manage energy and nutrient metabolism. Similarly, it has been reported that adipokines such as leptin and adiponectin are also secreted from brown/beige adipocytes. However, because of their very small mass relative to WAT, brown/beige adipocytes are likely to contribute little to human blood levels of leptin and adiponectin. In recent years, it has been understood that brown adipose tissue is not only involved in thermogenesis but also secretes endocrine factors called "batokines", which have important contributions to the metabolic health of our body. It has been shown that these batokines have autocrine, paracrine or endocrine effects. Some of the important batokines are as follows: Neuregulin 4, insulin-like growth factor-1 (IGF-1), fibroblast growth factor 21 (FGF21), and interleukin-6 (IL-6), fibronectin type III domain-containing protein 5 (irisin/FNDC5), ependymin-related protein 1 (EPDR1), C-X-C motif chemokine ligand-14 (CXCL14), (Fisher et al., 2012; Wang and Wahl, 2014; de Jong et al., 2015; Gunawardana and Piston, 2015; Cereijo et al., 2018; Deshmukh et al., 2019; Gaspar et al., 2021). One of these batokines, neuregulin 4, suppresses hepatic lipogenesis (Wang and Wahl, 2014). FGF21 and IL-6 stimulate brown/beige adipocyte thermogenesis by paracrine or autocrine pathway (Hondares et al., 2010; Fisher, 2012; Knudsen et al., 2014). It is believed that the level of IGF-1 increases in mice with type 1 diabetes who underwent BAT transplantation, thereby plays a role in reducing hyperglycemia (Gunawardana and Piston, 2015). EPDR1, which is defined as a new batokine, has been reported to have a great contribution to energy homeostasis in mice, in addition to having a role in adipocyte thermogenic differentiation. In addition, since EPDR1 is detected in human plasma, it also suggests that it has important contributions to human metabolism (Deshmukh et al., 2019). CXCL14 has been demonstrated to mediate brown fat-macrophage communication in thermogenic adaptation. CXCL14 has been shown to improve glucose homeostasis and induce browning in WAT in obese mice. (Cereijo et al., 2018).

3. BROWNING AGENTS

Beige adipocytes are found in WAT and have a WAT-like phenotype, but when induced they acquire a BAT-like phenotype with an increased capacity for thermogenesis. This phenomenon is called browning (Bargut et al., 2017). Browning of the WAT means that transcription factors such as PRDM16 and PPAR-α, and especially UCP-1, which is the hallmark of thermogenesis, should be expressed in white adipose tissue (Wu et al., 2013). Until now, in addition to stimuli such as exposure to cold, exercise, thyroid hormones, various hormones such as leptin, melatonin; pharmacological agents such as (PPAR) agonists; Plant-based substances such as capsaicin, resveratrol, curcumin have been shown to induce WAT browning or protect against HFD-induced obesity. It has also been observed that blocking some genes or overexpressing some genes have similar effects. Many agents have been tried for this purpose, especially in recent years, and many of them have been found to have significant effects on browning and against HFD-induced obesity (Wankhade et al., 2016; Kaisanlahti and Glumoff, 2019).

The number of browning agents is increasing very rapidly. In this part of our review, we will mention some of the important browning agents reported in the literature so far. Table 1 shows the list of browning agents. Cold exposure is the stimulus that we will describe as the most well-known and most

studied and even the oldest agent that causes the browning of WAT (Cousin et al., 1992). Similarly, β-3 AR agonists are another important group of browning agents. β-3 AR agonist CL 316243 has been shown to induce the development of brown adipocytes in conventional WAT depots, such as mesenteric, epididymal, inguinal, and retroperitoneal fat depots. (Ghorbani and Himms-Hagen, 1997). Increased expression of UCP1 in periovarian WAT depots has been observed in rodents with treatment with BRL 26830A (Chapman et al., 1988)

The potential impact of exercise on the induction of browning remains controversial, as previous studies in humans and rodents have reported negative reports of exercise for BAT activation and WAT browning (Segawa et al., 1998; Shibata and Nagasaka, 1987). On the other hand, studies in recent years have shown that exercise increases the expression of PGC-1α. In addition, irisin, an exercise-associated adipomyokine, has been shown to induce browning in humans and rodents (Bostrom et al., 2012).

It is well known that many different hormones, primarily thyroid hormones, can induce WAT browning (Weiner et al., 2017). Parathyroid hormone (PTHr) (Thomas and Mitch, 2017), glucagon like peptide 1 (GLP1) (Lopez et al., 2015), leptin (Dodd et al., 2015), melatonin (Jiménez-Aranda et al., 2013), and natriuretic peptides (NPs) also showed effects on WAT browning and BAT metabolism by several different mechanisms (Liu et al., 2018; Bordicchia et al., 2012) Moreover, in a recent report, maternal secretin promoted white adipose tissue browning in offspring (Xue et al., 2022). Batokines such as FGF21 (Fisher et al., 2012) IL-6 (Kristóf et al., 2019) and apelin (Than et al., 2015) have also demonstrated browning of WAT effects. In addition, several metabolites including, lactate, β-hydroxybutyrate (Carriere et al., 2014) and retinoic acid (Wang et al., 2017) have also shown browning effects on WAT.

To date, studies in mice or in vitro have shown that many plant-based compounds, most of which are in our diet, have WAT browning effects. These compounds are found in the foods we eat, and the use of these compounds in the treatment of obesity is a very smart strategy since they do not produce side effects compared to pharmacological drugs. Some important ones of these compounds are mentioned below. In studies with mice, capsaicin and related capsinoids have been reported to induce WAT browning through many different mechanisms (Baskaran et al., 2016). Similar browning effects have also been observed in the plant-based compound including resveratrol (Azhar et al., 2016), berberine (Zhang et al., 2014), decaffeinated green tea extract (Chen et al., 2017), cinnamon (Kwan et al., 2017), curcumin (Lone et al., 2016), quercetin (Lee et al., 2017). Furthermore, fish oil intake leads to upregulation of UCP-1 and the β3-AR in inguinal WAT of mice (Kim et al., 2015). In addition to the above compounds, natural bioactive constituents from herbs and nutraceuticals, which have effects on white adipose tissue browning, were reviewed in a recent review by Ma et. al (2022).

MiRNAs such as miRNA-32 (Ng et al., 2017) and miRNA-455 (Zhang et al., 2015) have also been reported to regulate both subcutaneous WAT browning and BAT activation. On the other hand, several miRNA types were found to be negatively regulated by BAT activity and WAT browning (Shamsi et al., 2017).

Various drugs have also been found to have effects on WAT browning. It was reported that a well-known agonist thiazolidinedione (TZD) compound, rosiglitazone induces browning of WAT in mice (Ohno et al., 2012). Similarly, Prostaglandin E2 (Garcia-Alonso and Claria, 2014) and Gleevec (Choi et al., 2016) showed similar effects on WAT Browning.

Table 1. Several agents used for the browning of white adipose tissue

Browning Agent	**Reference**	**Browning Agent**	**Reference**
Cold exposure	Cousin et al., 1992	***Hormones***	
β-3 adrenergic receptor agonists		Thyroid hormones	Weiner et al., 2017
CL 316243	Ghorbani and Himms-Hagen, 1997	Parathyroid hormone (PTH)	Thomas and Mitch, 2017
BRL 26830A	Chapman et al.,1988	Glucagon-like peptide 1 (GLP1)	Lopez et al., 2015
Dietary factors		Leptin	Dodd et al., 2015
Capsaicin	Baskaran et al., 2016	Melatonin	Jimenez-Aranda et al., 2013
Resveratrol	Azhar et al., 2016	Natriuretic peptides (NPs)	(Bordicchia et al., 2012; Liu et al. 2018
Berberine	Zhang et al., 2014	Maternal secretin	Xue et al., 2022
Green tea	Chen et al., 2017	Irisin	Bostrom et al., 2012
Fish oil	Kim et al., 2015	***Batokines***	
Quercetin	Lee et al., 2017	FGF21	Fisher et al., 2012
Curcumin	Lone et al., 2016	IL-6	Kristóf et al., 2019
Cinnamon	Kwan et al., 2017	Apelin	Than et al., 2015
MicroRNAs		***Metabolites***	
miRNA-32	Ng et al., 2017	Lactate	Carriere et al., 2014
miRNA-455	Zhang et al., 2015	β-hydroxybutyrate	Carriere et al., 2014
Drug agents		Retinoic acid	Wang et al., 2017
Thiazolidinediones (TZDs)	Petrovic et al., 2010	***Other factors***	
Prostaglandin E2	Garcia-Alonso and Claria, 2014	Gut microbiota	Moreno-Navarrete and Fernandez-Real, 2019
Gleevec	Choi et al., 2016		

The relationship between the gut microbiota and browning of WAT and also the activity of BAT has been reviewed by Moreno-Navarrete and Fernandez-Real (2019). Both the amount and composition of the gut microbiota have important effects on energy expenditure. Exposure to cold, calorie restriction and intermittent fasting cause changes in GUT microbiota composition, resulting in browning of WAT and increased BAT activity. Moreover, depletion of the microbiota has also been shown to activate the browning process in subcutaneous fat. (Suárez-Zamorano et al., 2015).

Finally, body conditions such as cachexia (Tsoli et al., 2012) and burns (Patsouris et al., 2015) can induce browning as well. In conclusion, the discovery of WAT browning has highlighted the importance of brown/beige adipose tissue targeted strategies to fight diseases such as obesity. With the discovery of new browning agents that have increased in recent years, promising results are expected in the treatment of obesity using dietary or pharmacological approaches (Bargut et al., 2017).

3.1. Nanomedicine-Based Strategies for Browning of WAT

In recent years, nanoparticles and transdermal patches have been used for the spesific delivery of browning agents to adipose tissue. In a recent review, nanomedicine based strategies for browning agent delivery have been summarized. We will focus on these delivery strategies. The many side effects as a result of the oral or injection administration of various browning agents have led researchers to find different delivery strategies. In this context, the tissue-specific drug delivery option seems to solve this problem. Various polymer nanoparticles such as poly(lactide-co-glycolide) (PLGA), poly(ethylene glycol) (PEG) and Polyethylenimine (PEI), and lipid nanoparticles (LNPs) and hepatitis B core (HBc) protein virus-like particles (VLPs) are used for these purposes (Zhang et al., 2021). In a recent study using resveratrol-loaded nanoparticles, trans-resveratrol was observed to significantly induce differentiation of adipose stromal cells (ASCs) into beige adipocytes after 5 weeks of intravenous administration to obese C57BL/6J mice. Similarly, a 40% reduction in fat mass was observed. In addition, it was accompanied by improved glucose homeostasis and reduced inflammation (Zu et al., 2021). In another study using peptide-functional nanoparticles containing rosiglitazone or a prostaglandin E_2 analog (16,16-dimethyl PGE_2), when injected into the adipose tissue vasculature of mice, both were found to stimulate the browning of WAT and angiogenesis (Xue et al., 2016).

Transdermal drug delivery is another option for specific delivery of browning agents to adipose tissue. Transdermal delivery of an agent allows a local, convenient, and painless alternative to oral and injectable administration. Various transdermal systems have been developed, such as microneedles and hydrogel patches, since the intrinsic physiological barrier of the skin is difficult to penetrate and consequently delivery efficiency is reduced. Similar strategies have been used for adipocyte browning Zhang et al., 2021; Zhang et al., 2018).

4. CONCLUSION

In conclusion, with the discovery of the browning of adipose tissue in humans, we have gained a new generation method to be used in the fight against obesity. Since the biology of beige adipocytes is a novel subject, the biochemical, genetic and physiological factors in these processes need to be analyzed and investigated comprehensively. Brown/beige adipocytes are a candidate to be a new-generation weight loss strategy and it is likely to have benefits against both obesity

and obesity-related metabolic diseases such as insulin resistance, diabetes, etc. Currently, there are numerous dietary compounds, various drugs and hormones, etc., which can be used as browning agents. However, in the future, with the development of a new generation of nanomedicine-based therapies, obesity can be treated by designing specific molecules that can bind directly to brown/beige adipocytes and activate thermogenesis. The therapeutic use of browning agents in people with obesity in the coming years will depend on the outcome of further randomised controlled trials.

Conflict of Interests "Authors declare no conflict of interests

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RESEARCH ARTICLE

CLASSIFICATION OF COVID-19 OMICRON VARIANT USING HYBRID DEEP TRANSFER LEARNING BASED ON X-RAY CHEST IMAGES

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Abstract

In 2019, the first case of COVID-19 was announced in China in Wuhan Province. Which led to the panic of the world and the declaration of a state of extreme emergency by the World Health Organization. Given that the world was in a state of crisis and closure, the use of deep learning technology provides speed and accuracy in diagnosing disease through chest images. Therefore, in this study, the dental X-Ray images of people infected with the omicron strain of Covid-19 virus were classified in comparison with a group of healthy people. In this study, we used 4 types of pre-trained deep learning algorithms in two ways, the first is using cross-validation and the second is the hybrid method by extracting the features from the models and then applying them to two types of deep learning algorithms (SVM and KNN). Accuracy results were obtained in the first scenario with a percentage of 94%, while in the second scenario, the accuracy results in the SVM classifier are higher than KNN with a difference of 5%, which is 92%. We also compared studies that used X-Ray images to classify COVID-19, as our results showed a clear superiority compared to other studies.

Keywords: Classification, CNN, SVM, KNN, Deep Transfer Learning, Feature Extraction

1. INTRODUCTION

Coronavirus was first detected in Wuhan, China in December 2019. The latest version of virus is a member of the "Coronaviruses family," which includes subgroups such as alpha, beta, gamma, and delta. In February 2020, the World Health Organization (WHO) designated the new version as "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2) COVID-19 (Khan, Shah et al. 2020, Lu, Stratton et al. 2020, Organization 2020, Zhu, Zhang et al. 2020). Covid-19 rapidly prevalence over the world, prompting WHO to declare a Global Pandemic on March 11, 2020, (Gorbalenya, Baker et al. 2020, Wu, Zhao et al. 2020, Zhou, Yang et al. 2020). Covid-19 mainly impacts the upper and lower respiratory tracts, and the virus is potentially lethal in persons with weakened immune systems (Lancet 2020, Razai, Doerholt et al. 2020). The Covid-19 most common contagious routes from person to person include physical contact, breathing, coughing, and sneezing (Al-Jumaili, Al-Azzawi et al. 2021, Al-Jumaili, Duru et al. 2021, Al-jumaili, Duru et al. 2022). Fever, headache, sore throat, and cough are the most prevalent Covid-19 symptoms (Guan, Ni et al. 2020, Huang, Wang et al. 2020, Li, Guan et al. 2020, Singhal 2020).

Deep learning using convolutional neural networks has recently been used to classify medical modality. X-Ray scans is the one of highly utilized forms of image for detecting Covid-19 using deep learning methodologies. These pictures are being utilized to diagnose problems caused by Covid-19 infection prior to therapy (Baltruschat, Nickisch et al. 2019, Zu, Jiang et al. 2020). GoogleNet (Szegedy, Liu et al. 2015), Xception (Chollet 2017), U-Net (Ronneberger, Fischer et al. 2015),AlexNet (Krizhevsky, Sutskever et al. 2012), VGG19 (Simonyan and Zisserman 2014), RestNet50 (He, Zhang et al. 2016), MobileNets (Howard, Zhu et al. 2017), DenseNet (Huang, Liu et al. 2017), and SqueezeNet (Iandola, Han et al. 2016) are examples of pre-trained deep learning models employed in the identification of Covid-19 in the current literature.

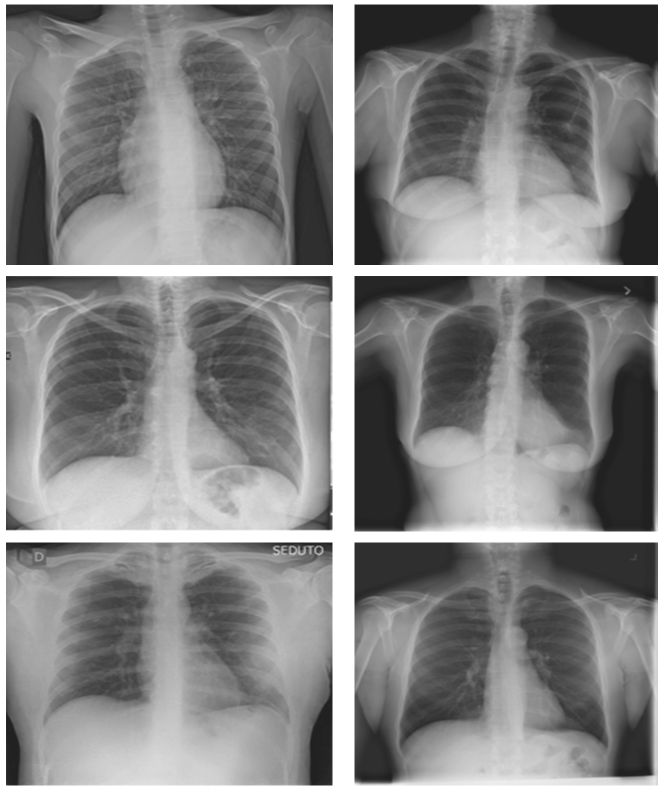
To diagnose various illnesses, several deep learning approaches are presented utilizing radiography and computed tomography datasets. In the (Liu, Cao et al. 2017)study created an improved CNN model that detects tuberculosis detection (TB) using an image dataset. Moreover, random sampling was utilized in the model to solve the problem of an imbalanced dataset, with the greatest accuracy being 85.68%. In (Dong, Pan et al. 2017), utilized an Xray dataset with various kinds of pre-trained models, involving ResNet, AlexNet, and VGG16. They used a pre-trained model with over 16000 photos as input for models. The binary classification achieved the highest precision of 82%, while the others had an accuracy of more than 90%. In (Chouhan, Singh et al. 2020),reported a 96% accuracy for pneumonia identification from X-Ray pictures after implementing an ensemble of AlexNet, DenseNet121, GoogLeNet, and ResNet18 with deep transfer learning. In (Hemdan,

Shouman et al. 2020), created a novel CNN model called the COVIDX-Net and compared seven different pre-trained deep learning models: VGG19, DenseNet121, InceptionV3, ResNetV2, Inception-ResNet-V2, Xception, and MobileNetV2. In (Khan, Shah et al. 2020), introduced a new CNN model called CoroNe, that uses the Xception architecture. The CoroNet was trained using an X-Ray image collection acquired from several publicly available sites for both Covid-19 and pneumonia. In (Wang, Lin et al. 2020), created COVID-Net, a novel CNN model that be able to identify the Covid-19 virus using publicly accessible X-Ray imaging datasets. In (Mahmud, Rahman et al. 2020), CovXNets was develop a new CNN model to implement several forms of classification for detecting COVID/normal/Viral/Bacterial pneumonia cases.

The purpose of this study is to explore the classification accuracy of Covid-19 impacted Chast X-Ray images for two types Covid-19 with Omicron variant and healthy. For this problem, four types of pre-trained CNN models used in order to classify these two classes. As a novelty, in the classification section, we applied two scenarios, first is by implement Cross-Validation. And second, features deduced from the last Convolutional layer to decrease the dimension of the input to two types of classifiers K-Nearest Neighbour (KNN) and Support Vectors Machine (SVM). Additionally, we adopted SVM to compare the classification performance of the KNN.

2. DATASET

Since Covid-19 is a novel condition, and the datasets are not immediately available and appropriate to be used for deep learning. As a result, we sought to identify a dataset that could be made freely available. We gathered Chest X-Ray images from Kaggle. At the moment of this present study, the database comprised of the positive case is 111, while negative is 230 and the number of the images is 230, the total images number of the images are 341 X-Ray with a size of 512×512px JPG. Figure 1 illustrates the sample of the image for both classes.



Omicron healthy

Figure 1. Sample images that were used in the study

3. METHODOLOGY

We choose many kinds of pre-trained models, which are namely ((GoogleNet, AlexNet, VGG16, MobileNet-V2, ResNet50, DenseNet201, ResNet18, Xception). We conducted out all by using MATLAB (R2021a) and workstations (GPU NVIDIA GeForce GTX 3080 8GB, Intel CPU i7-11800 @2.30HZ, RAM 32 GB). The last completely layer has been replaced with a new one in order to classify only binary classes. The InitialLearnRate set at 0.00001, the Validationfrequency to 30, MiniBatchSize to 20, and the MaxEpochs to 40 for-all pre-trained models. We have applied a Stochastic Gradient Descent with Momentum (SGDM) optimizer. Order to prevent over-fitting, we utilized a 5-fold cross-validation approach. The dataset was divided among training and testing with ratio is 70:30 ratio. For each of the five portions. The average outcomes from five graded folds of testing results utilized to establish to check the final performances of each model.

4. EVALUATION METRICS

Using the confusion matrix results from the validation tests, we employed several sorts of performance assessment criteria to examine every model independently. The confusion matrix

data were utilized as input to validate measures such as Accuracy, Sensitivity, Specificity, Precision, Negative Predictive Value (NPV), F1-Score, and Matthew's correlation coefficient (MCC), as well as the receiver operating characteristic curve. As demonstrated in Eq. 1, accuracy is determined as the number of true predictions from the entire dataset. The sensitivity is computed by subtracting the number of true positive (TP) predictions from the overall of positive predictions Eq. 2. The true negative (TN) prediction produced from all over the negatives in the dataset so-called true negative rate (TNR) Eq. 3.

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN} \tag{1}$$

$$Sensitivity = \frac{TP}{TP + FN} \tag{2}$$

$$Specificity = \frac{TN}{TN + FN} \tag{3}$$

Eq. 4 illustrates the precision (Positive Predictive Value (PPV)) as a proportion of true positive predictions to the overall number of positive predictions. While the negative predictive value (NPV) is provided in Eq. 5, The harmonic mean, often called the F1-score, will be calculated based on accuracy and sensitivity, as stated in the Eq. 6. In the end, the correction coefficient is calculated through the Matthew's correlation coefficient range (MCC) from Eq. 7.

$$precision(PPV) = \frac{TP}{TP + Fp} \tag{4}$$

$$\text{negative predictive value } (NPV) = \frac{TN}{TN + FN} \tag{5}$$

$$F1 - score = \frac{2 * TP}{2 * TP + FP + FN} \tag{6}$$

$$MCC = \frac{(TP * TN) - (FP * FN)}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}} \tag{7}$$

5. RESULTS

In this section, we used four diverse types of CNN models to classify Omicron virus. We also used, two scenarios of classifiers: the first on using SoftMax classifiers which is the standard one used in the architecture of these models, second is a hybrid technique based on extract the features from CNN models and applying them to the supervised machine learning classifiers, namely (support vector machine (SVM) and K-nearest neighbors algorithm (KNN)).

For the first scenario, as shown in the Figure 2, the result that we achieved from the confusion matrix used to calculate the result and check the performance of each model with different scenarios is shown. It is clear that the ResNet50 obtained the highest results for all evaluation matrices, while the ResNet18 also showed good results compared with two other types of CNN models. All the results shown in the Table 1, which illustrate the performance of all models that applied in this study.

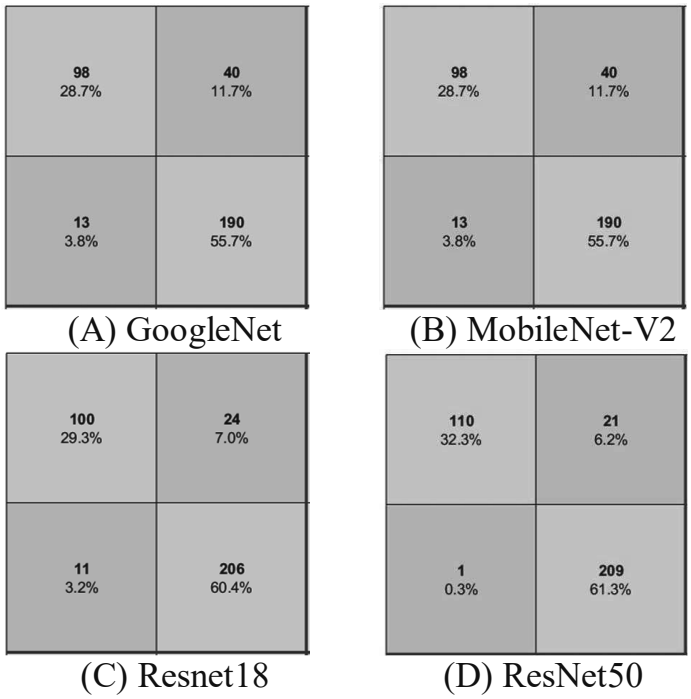


Figure 2. Result of confusion matrix by using SoftMax classifier

Table 1. performance of CNN models using SoftMax Classifier

Classifier Types	Dataset	Model	Evaluation Metrics						
			Accuracy	Sensitivity	Specificity	Precision	NPV	F1-Score	MCC
SoftMax	X-Ray	GoogleNet	0.84	0.71	0.93	0.88	0.82	0.78	0.67
		MobileNet-V2	0.71	0.56	0.79	0.57	0.78	0.56	0.35
		ResNet50	**0.94**	**0.84**	**1.00**	**0.99**	**0.91**	**0.91**	**0.87**
		ResNet18	0.90	0.81	0.95	0.90	0.90	0.85	0.78

In the second scenario, we applied the hybrid method by extracting features from a fully connected layer and using them as inputs to SVM and KNN. Figure 3 shows the results obtained from the confusion matrix using the CEPSIB algorithm, and Figure 4 shows the results of the confusion matrix obtained using KNN.

As shown in these two types, the results obtained using the SVM algorithms were also good and close to the results in the first scenario, where the advantages that were obtained using the ResNet18 algorithm had the highest results compared to the other advantages that were applied to the same algorithm which illustrate in the Table 2.

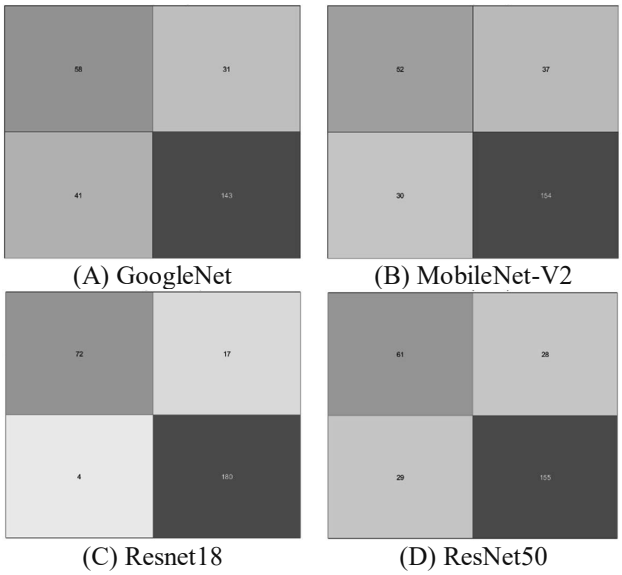


Figure 3. Result of confusion matrix by using feature extracted form CNN models and applied to SVM classifier

Table 2. Performance of CNN models using SVM Classifier

Classifier Types	Dataset	Model	Evaluation Metrics						
			Accuracy	Sensitivity	Specificity	Precision	NPV	F1-Score	MCC
SVM	X-Ray	GoogleNet	0.74	0.65	0.78	0.59	0.82	0.62	0.42
		MobileNet-V2	0.75	0.58	0.84	0.63	0.81	0.61	0.43
		ResNet50	0.79	0.69	0.84	0.68	0.85	0.68	0.53
		ResNet18	**0.92**	**0.81**	**0.98**	**0.95**	**0.91**	**0.87**	**0.82**

Table 3 shows the results obtained by using the KNN algorithm, which shows that again the highest result was obtained using the features obtained by Resent 18, although the results are less than the previous algorithm (SVM), but it is clear that the classification of the virus Omicron is possible using the two methods that have been suggested using chest X-Ray.

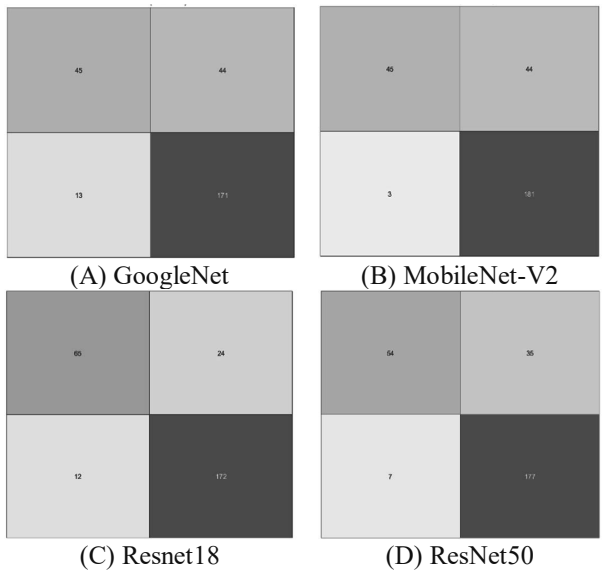


Figure 4. Result of confusion matrix by using feature extracted form CNN models and applied to KNN classifier

Table 3. performance of CNN models using KNN Classifier

Classifier Types	Dataset	Model	Evaluation Metrics						
			Accuracy	Sensitivity	Specificity	Precision	NPV	F1-Score	MCC
KNN	X-Ray	GoogleNet	0.79	0.51	0.93	0.78	0.80	0.61	0.50
		MobileNet-V2	0.83	0.51	0.98	0.94	0.80	0.66	0.60
		ResNet50	0.85	0.61	0.96	0.89	0.83	0.72	0.64
		ResNet18	**0.87**	**0.73**	**0.93**	**0.84**	**0.88**	**0.78**	**0.69**

Finally, we compared our findings with other pioneering work on COVID-19 classification of X-ray datasets recently published in the literature. As shown in Table 5, our results clearly outperformed the studies in which different techniques were used for classification, as the best accuracy results obtained are shown in bold.

Table 4. Comparison of state-of-the-art deep learning model results with our proposed methods

Ref.	Dataset	Image Types	DL Model	Layers Num.	Classifier	Accuracy %
(Hemdan, Shouman et al. 2020)	Cohens GitHub	X-Ray	COVIDX-Net	Standard	SoftMax	90
(Khan, Shah et al. 2020)	Different Datasets	X-Ray	Coronet	Modified	SoftMax	89.5
(Basu, Mitra et al. 2020)	Different Datasets	X-Ray	CNN	12	Grad-CAM	90.1
(Khobahi, Agarwal et al. 2020)	COVIDx	X-Ray	Coronet	2 separates (FPAE) + ResNet18	SoftMax	93.50
(El Asnaoui and Chawki 2020)	Different Datasets	X-Ray, CT-scan	Inception-ResNetV2	Standard	MLP Classifier	92.18
(Hall, Paul et al. 2020)	Different Datasets	X-Ray	Resnet50, VGG16	Modified	Snapshot Ensembles	91.24
(Rahimzadeh and Attar 2020)	Different Datasets	X-Ray	Xception, ResNet50V2	Modified	SoftMax	91.04
(Goodwin, Jaskolski et al. 2020)	Different Datasets	X-Ray	mobilenetv2, Densenet121, Resnet (18,50,101,152), Densenet (169,201), Resnext50, wideresnet (50,101) Rresnext101	Modified	SoftMax	89.4
(Khalifa, Smarandache et al. 2021)	Different Datasets	X-Ray	GoogleNet	Standard	SoftMax	73.12
(Moutounet-Cartan 2020)	Different Datasets	X-Ray	VGG16	Modified	SoftMax	84.1
present	**Kaggle**	**X-Ray**	**ResNet50**	**Modified**	**SoftMax**	**94**

6. CONCLUSION

The classification of diseases is one of the most important pioneering topics in the current era because of its direct impact on the speed of diagnosis and the high accuracy in determining the type of disease. The deep learning algorithm has been used in many diseases for classification, and this indicates the positivity offered by deep learning techniques and the high impact on classification.

In this study, the Omicron virus, which is the new strain of Corona virus, was classified. In view of what has happened in the last few years and the damage done to human society by the previous Delta dynasty, which killed many countries and led to the collapse of their health sectors and the death of many people. Therefore, in this study, we used chest X-Ray images of people infected with the Omicron Covid virus with healthy people. We used pre-trained models to classify the images. We also used to work on a hybrid method between deep learning and machine learning algorithms, by extracting features from images and using them as inputs to the machine learning algorithm.

In the first scenario, where the highest results obtained using the Resent 50 was 94% of accuracy, while in the second scenario (hybrid) the highest accuracy was obtained using the characteristics extracted by the Resent 18 model in the two algorithms (SVM and KNN), which is 92 % and 87 %. In order to verify the validity of the results obtained, we compared our results with the results of other recently published studies that also use X-Ray images. It is very clear that the results obtained by the proposed method significantly outperformed the other studies.

We can conclude that the use of these dental images with deep learning techniques has obtained higher results than the hybrid method, and that is why deep learning methods provide the possibility of analyzing the images with extreme accuracy. Since in the future we can develop an algorithm that can provide higher results than the results of the pre-trained model.

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RESEARCH ARTICLE

EXPLANATION OF MORTALITY RATES WITH SOCIO-ECONOMIC INDICATORS

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Abstract

This study aims to examine the relationship between death rates and socioeconomic variables and to develop policy recommendations to reduce mortality rates. Therefore, the variables of maternal mortality rate, crude mortality rate, and infant mortality rate are explained with real health expenditures per capita, number of nurse midwives, total health expenditures, number of physicians, and number of hospitals. The most recent data available between 2002 and 2019 are used in the article. Data are taken from health statistics annually. While three different mortality rates are considered as dependent variables in the study, five different variables indicating socioeconomic status are used as independent variables. Since more than one dependent and independent variable is used, canonical correlation analysis is preferred as the method. In the results of the analysis, it has been revealed that there is a high relationship between maternal mortality rate, infant mortality rate, crude death rate, and the number of hospitals, the number of nurses-midwives, the number of physicians, total health expenditures and per capita health expenditures. According to this, it is important to increase health awareness, increase the quality of health services in society, and facilitate access to health services. In addition, it is recommended to increase the number of health workers, improve health literacy in society and increase investments in the field of health.

Keywords: Canonic correlation analysis, mortality rate, socio-economic indicators, statistical analysis.n

1. INTRODUCTION

According to the definition of the World Health Organization (WHO), health is not only the absence of infirmity and disease but also a state of complete physical, mental and social well-being (WHO, 2006:1). Health is the basic need of every individual. Without your health, other goods and services have no value. Due to the desire of individuals to live healthy lives, the demand for health services is increasing. With the increase in demand, discussions about health services have increased (Witter, 2002:4). The World Health Organization defines that the main purpose of health systems is to improve, renew and maintain health (WHO,2000).

Maternal mortality rate, infant mortality rate and total death rate show a country's development level. While the death rate is low in developed countries, this rate is high in developing and underdeveloped countries. Reducing the death rate will both improve the health status of the country and increase the level of development of the country. Mortality is an indicator of development. The decrease in this rate shows the success of health and development programs (F., Lorcu, B., Acar Bolat, 2009). Thanks to the policies aimed at reducing the death rate, the life span of society will be extended and the quality of life of the people will increase.

Therefore, the variables of maternal mortality rate, crude mortality rate and infant mortality rate are explained as the real health expenditures per capita, the number of nurse midwives, the total health expendıtures, the doctors per 1,000 people and the number of hospitals. The most up-to-date data available for the years 2002-2019 are used. The data are taken from the statistical annuals of the Turkish Statistical Institute and the Ministry of Health.

In Turkey's 2002 data, while the maternal mortality rate was 39 per 100000 people, it decreased to 13.1 in 2019. Similarly, the infant mortality rate was 27.5 in 2002, it reduced to 8.5 in 2019. However, the paternal mortality rate increased from 16.8 in 2002 to 18.4 in 2020.

More than one dependent and independent variable is used in the study. For this reason, "canonical correlation analysis" is preferred to reveal the relationship. Canonical Correlation Analysis (CCA) is used to examine the relationship between two sets of variables.

As a result of the CCA; the maternal mortality rate provides the greatest contribution to the first dependent canonical variable from mortality rates. The second largest contributor to the canonical variable is infant mortality rates. The crude death rate provides the lowest contribution.

2. LITERATURE

Hertz et al. (1994) considered life expectancy at birth, infant mortality rate and maternal mortality rate as dependent variables in their study. Nutritional factors, percentage of households without clean water and total literacy level are important variables in determining infant mortality rate. According

to the results of the analysis, maternal mortality rate and total energy consumption and excess energy consumption variables are significantly related.

Zakir and Wunnava (1999) aimed to determine the factors affecting infant mortality rate by using data from 112 countries in their study. They emphasize that Gross Domestic Product (GDP) and female literacy rate have a large impact on the infant mortality rate. However, they revealed that healthcare expenditures did not affect the infant mortality rate.

Liu (2007) investigated the effect of per capita income and hospital birth rate on maternal mortality rate in counties of China. Two variables were found to be effective on maternal mortality rate. She concluded that the maternal mortality rate is 100.9 per 100000 live births in low-income districts, and 68.1 per 100000 live births in high-income districts.

Schell et al. (2007) explained the infant mortality rate with socioeconomic indicators (female literacy rate, per capita GDP, Gini index, public health expenditures, poverty rate). They analyzed data from 152 low-, middle- and high-income countries using regression analysis. In low-income countries, the female literacy variable was found to be more important than the GDP variable. The Gini index is significant in middle-income countries but insignificant in high-income countries.

Farahani et al. (2009) worked with a dataset of 99 countries at 5-year intervals between 1960 and 2000. They investigated the effect of changes in the number of doctors per capita on infant mortality in the short term and long term. In the study, it is concluded that if the number of available doctors is doubled, infant mortality rates are reduced by 15% in the short term and 50% in the long term.

Lorcu and Bolat, (2009) examined the relationship between death rates by age and socio-economic indicators with canonical correlation analysis. While death rates by age were used as a dependent variable, socio-economic indicators were used as independent variables. According to the results of the study, infant, under-five, 5-14 and over 60-year-old mortality rates are highly correlated with literacy, unemployment and GDP per capita.

Suriyakala (2016) aimed to determine the factors affecting the infant mortality rate by using the variables of fertility rate, national income, women in labour force, expenditure on health care. The data were analyzed with the regression model. It made recommendations to reduce mortality rates.

Azuh et al. (2017) aimed to determine the non-medical factors that may be effective in maternal death. A survey was conducted with 360 randomly selected individuals from rural and semi-rural communities in Nigeria. They said that strengthening maternal health services and the status of women can be effective in reducing maternal mortality rates.

Baraki (2020) worked with 2016 Ethiopian data. Infant mortality was explained by the variables of infant gender, mass birth and premature birth. Data were analyzed using a multivariate logistic regression model. He revealed that baby gender and mass births are effective on infant mortality.

Lamichhane et al. (2017) used the 2006 and 2011 datasets in the Nepal Demographic and Health Surveys. Two surveys were conducted to explain infant mortality. Multistage stratified cluster sampling techniques were used in the study. The ecological region, next birth interval, breastfeeding status and maternity assistance were determined as important determinants of infant mortality. Babies born with professional help have a lower risk of death. They found that infants who never received breast milk had a higher risk of death.

In the studies we examined in the literature, mortality rate variables are generally explained with socio-economic indicators, education, employment, population, and health services indicators. In our study, we explained mortality rates with socio-economic and health services indicators.

3. MATERIAL AND METHODS

In the study, variables of maternal mortality rate, crude mortality rate, and infant mortality rate are explained with real health expenditures per capita, number of nurse midwives, total health expenditures, number of physicians, and number of hospitals. In the article, canonical correlation analysis is preferred as the method. Because more than one dependent and independent variable is used.

3.1. Data

In the study, the most recent data available between 2002 and 2019 years are used. The variables in table 1 are used in the article.

Table 1. Variables

Dependent Variables	**Independent Variables**
Infant Mortality Rate	Total Health Expenditures
Maternal Death Rate	Per Capita Health Expenditures
Crude Death Rate	Number of Nurses-Midwives
	Number of Physicians
	Number of Hospitals

Infant mortality refers to infants who die under 1 year of age. The infant mortality rate gives the number of infants who die per 1000 live births in a year (Tüylüoğlu and Tekin, 2009). It is calculated by dividing the total number of babies born that year by the number of babies born that year and multiplying by 1000. This rate is one of the most important parameters that show the health, development, and

mother-child health status of a country. It is one of the most important success criteria of the health system (Aydın and Aba, 2018).

Maternal death is the death that occurs during pregnancy, during childbirth or 42 days (6 weeks) after birth from any cause within a year. The maternal mortality rate is calculated by dividing the number of female deaths during pregnancy, childbirth, and puerperium by the number of females aged 15-49 and multiplying by 100000 (Tezcan, 2017). The maternal mortality rate determines the level of women's health in society. It is an important criterion that shows whether the services in this area are sufficient or not.

The crude death rate is calculated from the number of deaths from disease or general causes. The rate is obtained from the number of deaths per 1000 people, usually calculated annually. It is calculated by dividing the number of deaths in a year by the population. The low mortality rate indicates the quality of health services in a country and the development of the country. Death rates provide information about socioeconomic status.

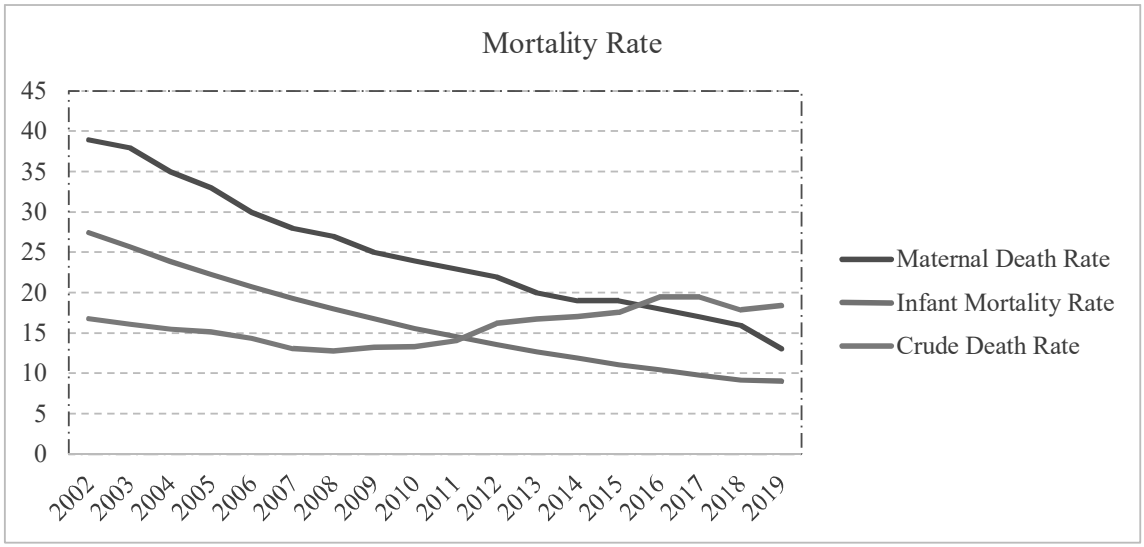

Figure 1. Mortality Rate

According to Figure 1, the maternal mortality rate decreased from 39 per 100,000 people in 2002 to 13.1 in 2019. While the infant mortality rate was 27.5 in 2002, it decreased to 8.5 in 2019. However, it is seen that the crude death rate increased from 16.8 in 2002 to 18.4 in 2019.

Health expenditures are expenditures made to provide the services necessary for a healthy society in a country. These expenditures include investments made not only for the healing of diseases but also

for the prevention of diseases that may occur (Loş, 2016). As the quality of life in individuals increases, the budget allocated to health expenditures also increases. Developed countries have high health expenditures (Atalan, 2018).

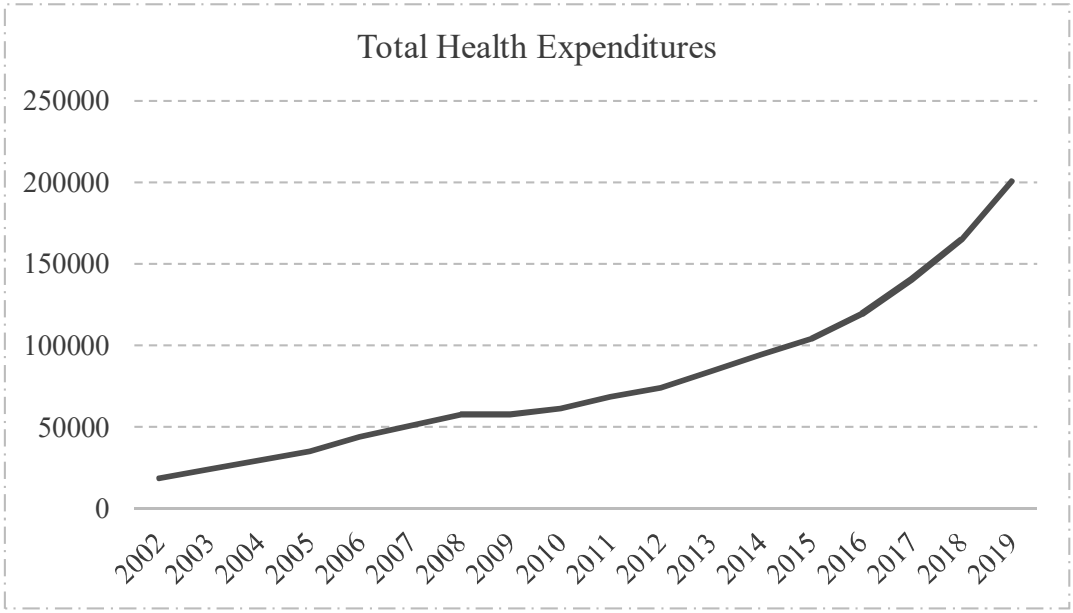

Figure 2. Total Health Expenditures

When Figure 2 is examined, total health expenditures increased from 18774 million in 2002 to 201031 million in 2019.

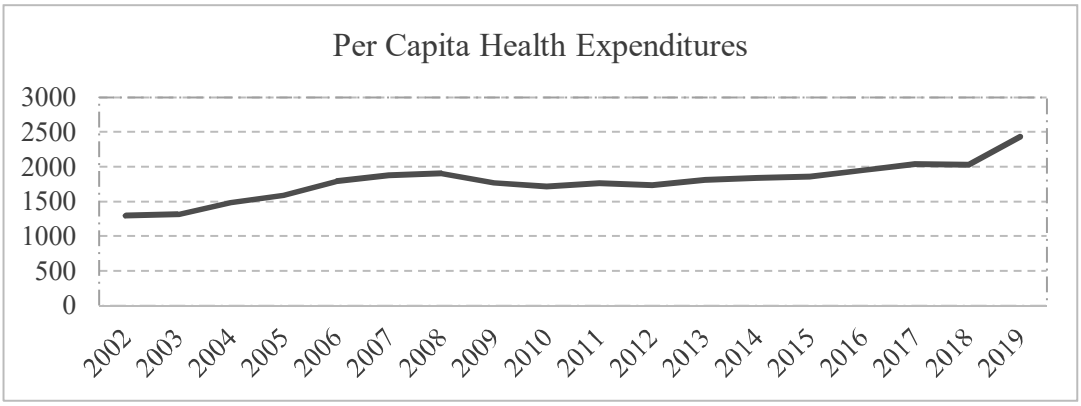

Figure 3. Per Capita Health Expenditures

While per capita health expenditures were 1294 million in 2002, it increased to 2434 million in 2019.

The first element of a society's health system is doctors, nurses and health technicians. For this reason, the education of doctors and other health workers is given importance in countries. The shortage in the number of doctors causes the effectiveness of the health system in the country to deteriorate. The increase in the number of doctors, nurses and midwives increases the level of health positively (Göztepe, 2017). One of the factors affecting the decrease in deaths is the quality of health services in the country. Health service is primarily based on trained manpower.

Social equality, which is one of the basic principles of health services, can be achieved by everyone receiving health services equally. To receive the service equally, there should be a sufficient number of doctors, nurses and midwives in health institutions.

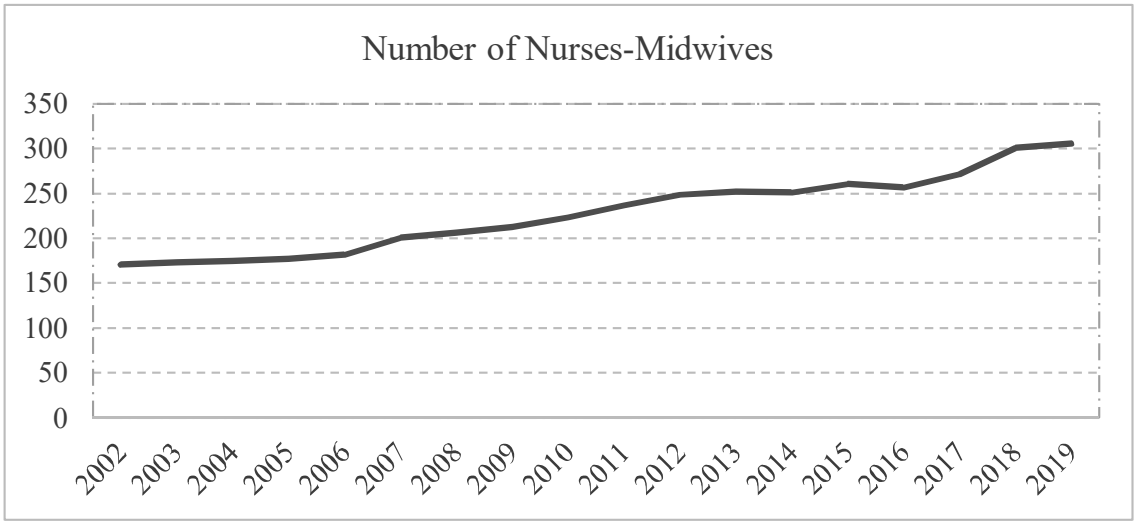

Figure 4. Number of Nurses-Midwives

When the graph is examined, it is seen that while the number of nurses-midwives per 100000 people was 171 in 2002, this rate was 342 in 2019.

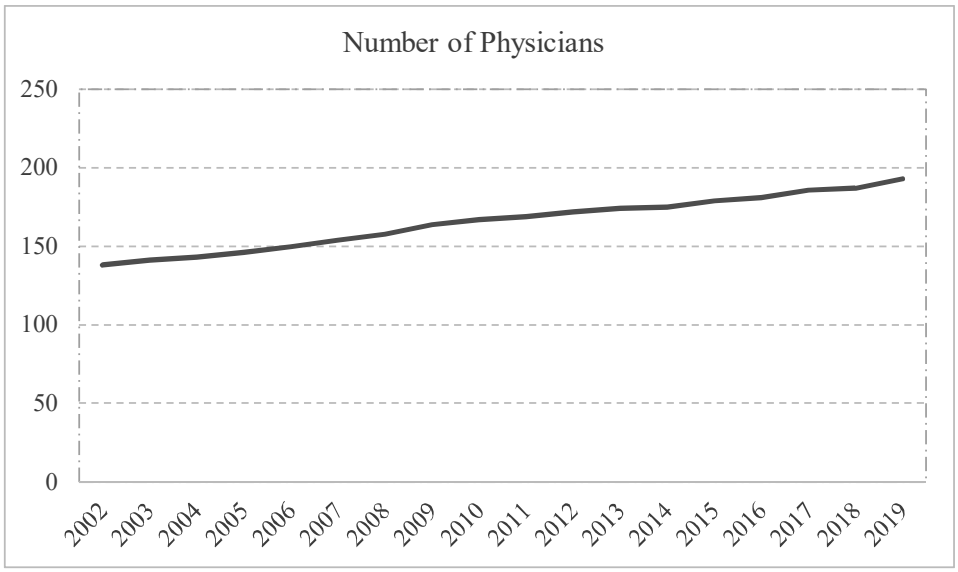

Figure 5. Number of Physicians (Per 1000 People)

It is seen that the number of physicians per 100000 people in 2002 was 138, and this number increased to 205 in 2019.

The number of hospitals should be sufficient to reach health services on time. More patients are reached through easier access to health services. Thus, the life span of individuals is extended and their quality-of-life increases.

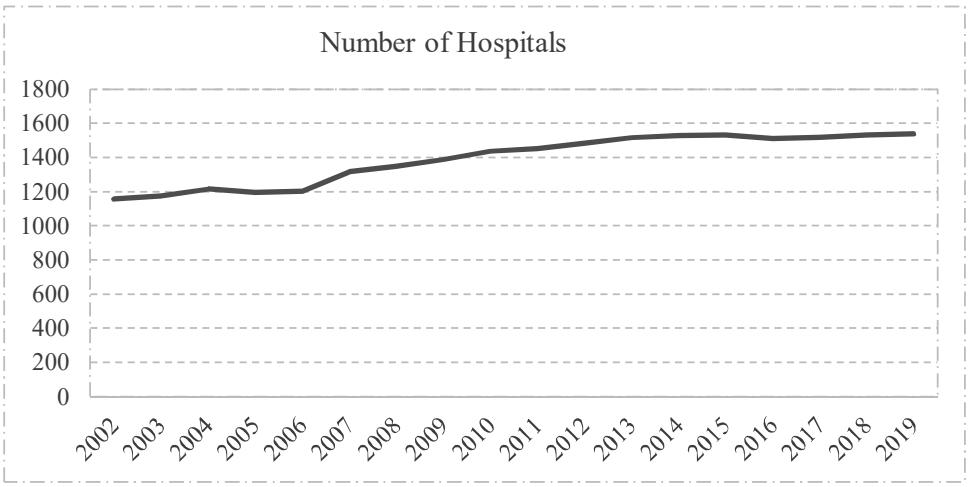

Figure 6. Number of Hospitals

In Figure 6, it is seen that while the number of hospitals was 1156 in 2002, this number increased to 1534 in 2019.

3.2. Canonic Correlation Analysis

Canonical Correlation Analysis (CCA) is one of the multivariate analysis methods. CCA is an extension of multiple regression analysis. In multiple regression analysis, the relationship between one dependent and more than one independent variable is investigated. Canonical correlation analysis is used when it is necessary to investigate the relationship between more than one dependent and more than one independent variable. CCA is accepted as a generalized form of multiple regression analysis (Levine, 1977). This analysis is used to examine the relationship between two sets of variables with many variables. It divides many variables into two subsets, allowing us to obtain a small number of linear components of the variable. Interpretation of the relationship between variables becomes easier (Lorcu, Bolat, 2009).

CCA does not require a dependent or independent relationship between two variable groups. However, we can use one group of variables as dependent and the other variable group independently. In this analysis method, one of the variable sets is considered as dependent and the other as independent. New variables are produced from linear combinations of variables in each set (Hair et al., 2010). These new variables are called canonical variables. It is aimed to maximize the correlation between new variables (Tabachnick and Fidell, 2007).

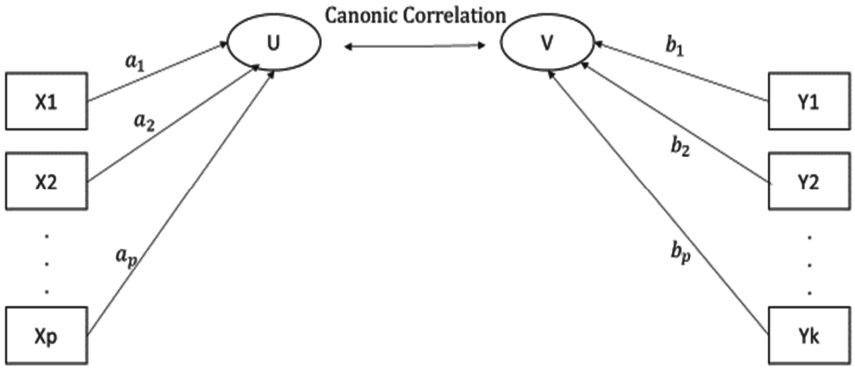

Figure 7. General Structure of Canonical Correlation Analysis

$$X = \begin{bmatrix} X1 \\ \vdots \\ Xp \end{bmatrix} \quad (1)$$

$$Y = \begin{bmatrix} Y1 \\ \vdots \\ Yq \end{bmatrix} \quad (2)$$

Canonical correlation analysis is derived from the linear components of independent variables (X) and p dependent variables (Y) consisting of n observations. (Tacq, 1999).

CCA is known as a powerful method to reveal the relationships between two sets of variables. This analysis method aims to find the linear functions of two variable sets in the form that will show the highest correlation.

$$bi1\mathrm{Yi1} + bi2\mathrm{Yi2} + \cdots + bip\mathrm{Yip}\ ai1\ Xi1 + ai2\ Xi2 + \cdots + aiq\ Xiq \quad (3)$$

The aip and biq coefficients represent the canonical weights.

Dependent and independent canonical variables are shown as follows (Levine, 1977).

$$U1=\alpha 11X1+ \alpha 12X2+...+ \alpha 1qXq \quad (4)$$

$$U2=\alpha 21X1+ \alpha 22X2+...+ \alpha 2qXq \quad (5)$$

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$$Us=\alpha s1X1+ \alpha s2X2+...+ \alpha sqXq \quad (6)$$

$$V1 = \beta 11Y1+ \beta 12Y2+ ...+ \beta 1pYp \quad (7)$$

$$V2 = \beta 21Y1+ \beta 22Y2+ ...+ \beta 2pYp \quad (8)$$

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$$Vs = \beta s1Y1+ \beta s2Y2+ ...+ \beta spYp \quad (9)$$

q is the number of variables belonging to the argument set.

p represents the number of variables belonging to the dependent variable set.

s represents the number of variables of the set with the fewest variables.

Ui is the independent canonical variable. It represents the linear combination of independent variables in the equation.

Vi is the dependent canonical variable. It expresses the linear combination of dependent variables.

In CCA, the number of variables in the data sets does not have to be equal. In the analysis, new variables are produced with linear composites of the variables located between two variable sets. The correlation between these new variables is aimed to be maximum and unit variance.

The first canonical function indicates the relationship between the first independent canonical variable (U1) and the first dependent canonical variable (V1). The correlation between U1 and V1 gives the maximum canonical correlation coefficient. The canonical correlation coefficient is calculated as follows (Press and James 1972).

The canonical correlation coefficient is calculated as follows (Press, 1984).

$$\mathrm{Cor}(U,V)=\frac{\mathrm{Cov}(U,V)}{\sqrt{(\mathrm{Var}(V)\ \mathrm{Var}(U)}} \tag{10}$$

Canonical correlation takes values between 0 and +1. Canonical correlation value of 1 indicates a perfect linear relationship between the two sets. A canonical correlation value between 0.9 and 1 indicates a very high relationship between sets, while a value between 0 and 0.25 indicates a weak relationship.

The square of the canonical correlation is equal to the "eigenvalue" (Tabachnick and Fidell, 2007). The eigenvalue indicates the size of the common variance between the dependent canonical variable and the independent canonical variable (Hair et al., 2010). It includes the rate of variance explained by the independent variable in the dependent variable and the rate of variance explained by the dependent variable in the independent variable (Tacq, 1999). Analysis results are interpreted with the help of "canonical weight", "canonical load", "canonical cross load", "explained variance ratio" and "redundancy index".

The simple linear correlation between the original variable and the canonical variable is called "canonical load" (Lattin et al., 2003). High correlation indicates that the contribution of the related variable to its canonical variable is strong. Canonical cross load; It refers to the simple linear correlation between the original dependent variables and the independent canonical variables, or the correlation between the original independent variables and the dependent canonical variables (Hair et al., 2010). It shows the strength of the contribution of the highly correlated variable to the canonical variable in the cross-set.

3.3. Analysis Results

The analysis is carried out with IBM SPSS 23 package program.

According to correlation analysis, it is seen that the relationship between maternal mortality rate, infant mortality rate and crude death rate, number of hospitals, number of nurses-midwives, number of physicians, and total health expenditures are high.

In table 2, there is no statistically significant relationship between crude death rate and per capita health expenditures. But there is a significant relationship between other variables and per capita health expenditures. In addition, these relationships are strong.

Table 2. Correlations Between Original Variables

(Pearson Correlation=Cor.) Sig. (2-tailed)		Maternal Death Rate	Infant Mortality Rate	Crude Death Rate	Per Capita Health Expenditures	Number of Nurses-Midwives	Total Health Expenditures	Number of Physicians	Number of Hospitals
Maternal Death Rate	Cor.	1	0.995	-0.473	-0.879	-0.960	-0.898	-0.988	-0.965
	Sig.		0.000	0.047	0.000	0.000	0.000	0.000	0.000
Infant Mortality Rate	Cor.	0.995	1	-0.493	-0.841	-0,957	-0,880	-0,988	-0,974
	Sig.	0.000		0.038	0.000	0.000	0.000	0.000	0.000
Crude Death Rate	Cor.	-0.473	-0.493	1	0.320	0.599	0.658	0.559	0.454
	Sig.	0.047	0.038		0.196	0.009	0.003	0.016	0.058
Per Capita Health Expenditures	Cor.	-0.879	-0.841	0.320	1	0.822	0.881	0.848	0.746
	Sig.	0.000	0.000	0.196		0.000	0.000	0.000	0.000
Total Health Expenditures	Cor.	-0.960	-0.957	0.599	0.822	1	0.950	0.983	0.938
	Sig.	0.000	0.000	0.009	0.000		0.000	0.000	0.000
Number of Nurses-Midwives	Cor.	-0.898	-0.880	0.658	0.881	0.950	1	0.929	0.811
	Sig.	0.000	0.000	0.003	0.000	0.000		0.000	0.000
Number of Physicians	Cor.	-0.988	-0.988	0.559	0.848	0.983	0.929	1	0.961
	Sig.	0.000	0.000	0.016	0.000	0.000	0.000		0.000
Number of Hospitals	Cor.	-0.965	-0.974	0.454	0.746	0.938	0.811	0.961	1
	Sig.	0.000	0.000	0.058	0.000	0.000	0.000	0.000	

After testing the significance of the canonical correlation coefficients, "canonical load" and "canonical cross load" results can be interpreted for meaningful functions. In the analysis, canonical correlations can be calculated as much as the number of variables in the set with the least number of variables (Tacq, 1999). Since there are 5 independent and 3 dependent variables in the study, the number of canonical functions and canonical correlation coefficient that can be calculated is 3.

According to the Barlett test calculated for the significance of the canonical correlation coefficient, Wilk's chi-square value shows χ^2 distribution in pxq degrees of freedom.

$H_0: \rho_1 = \rho_2 = \rho_3$ (Canonical correlations all equal zero)

H_a At least one is nonzero

When the H_0 hypothesis is rejected, the largest canonical correlation coefficient is subtracted from the hypothesis. The process is continued until the canonical correlation coefficients are not significant or until all the variables are exhausted (Tacq, 1999). H_0 hypothesis is rejected when probability value $< \alpha=0.05$.

First, the results of the significance test of these three canonical correlations should be checked. When we look at the significant value according to the Wilks Lambda test result in the SPSS analysis output (Table 1), it is seen that the probability values of the three canonical variables are below 0.05. That is, all canonical correlations are statistically significant and can be interpreted. The first canonical correlation coefficient is (0.997). In the second canonical function, the relationship between the dependent and independent canonical variable (0.856) and the third canonical correlation coefficient (0.723) are calculated.

Tablo 3. Canonical Correlations

	Correlation	Wilks Statistic	F	Sig.
1	0.997	0.001	24.584	0.000
2	0.856	0.127	4.953	0.001
3	0.723	0.478	4.377	0.027

$$v1 = -0.98y1 - 0.032y2 - 0.026y3 \quad (11)$$

$$v2 = 1.063y1 - 0.559y2 + 1.117y3 \quad (12)$$

$$v3 = 10.146y1 - 10.363y2 - 0.359y3 \quad (13)$$

$$u1 = 0.306x1 + 0.082x2 - 0.297x3 + 0.74x4 + 0.191x5 \quad (14)$$

$$u2 = -2.129x1 - 2.665x2 + 3.712x3 + 0.76x4 + 0.379x5 \quad (15)$$

$$u3 = -1.145x1 - 0.295x2 - 1.87x3 + 3.633x4 - 0.648x5 \quad (16)$$

When the canonical loads belonging to the dependent set are examined, maternal mortality rate (-1.000) provides the greatest contribution to the first dependent canonical variable among the mortality rates. It provides the second largest contribution to the canonical variable (0.454) and the lowest contribution.

Crude death rate with 0.890 provides the biggest contribution to the second dependent canonical variable among mortality rates. Infant mortality rate makes a low contribution to the canonical variable at the rate of -0.052. Maternal mortality rate, on the other hand, provides the lowest contribution with -0.22.

When we examine the contributions made to the third dependent canonical variable, infant mortality rate made the highest contribution with -0.091. However, it has a very low contribution compared to the first and second canonical variables.

Table 4. Set 1 Canonical Loadingsand Cross Loadings

	Set 1 Canonical Loadings			**Set 1 Cross Loadings**		
Variable	1	2	3	1	2	3
Maternal Death Rate	-1.000	-0.022	0.004	-0.997	-0.019	0.003
Infant Mortality Rate	-0.995	-0.052	-0.091	-0.992	-0.045	-0.066
Crude Death Rate	0.454	0.890	-0.049	0.453	0.762	-0.036

When the cross canonical loads of the dependent set are examined, similarly, maternal mortality rate (-0.997) made the highest contribution in the first canonical variable. Crude Death Rate (0.762) made the highest contribution to the second canonical variable. Infant Mortality Rate (-0.066) made the highest contribution to the third canonical variable.

According to the canonical loads of the independent set, the first independent canonical variable provides the largest number of physicians (0.988). Subsequently, the number of hospitals (0.967), the number of nurses-midwives (0.959), total health expenditures (0.893), per capita health expenditures (0.883) variables contribute to the canonical variable, respectively.

Table 5. Set 2 Canonical Loadings and Cross Loadings

	Set 2 Canonical Loadings			**Set 2 Cross Loadings**		
Variable	1	2	3	1	2	3
Per Capita Health Expenditures	0.883	-0.125	-0.436	0.880	-0.107	-0.315
Number of Nurses-Midwives	0.959	.214	-0.050	0.956	0.183	-0.036
Total Health Expenditures	0.893	0.318	-0.308	0.891	0.272	-0.223
Number of Physicians	0.988	0.147	0.011	0.986	0.126	0.008
Number of Hospitals	0.967	0.031	0.198	0.965	0.027	0.143

While total health expenditure (0.318) contributed the most to the second independent canonical variable, the second largest contribution is made by the number of nurses-midwives (0.214).

Health expenditure per capita (0.436) is made the highest contribution to the third independent canonical variable, total health expenditure (-0.308) is made the second largest contribution.

When the cross canonical loads of the independent set are examined, the highest contribution to the first canonical variable is Health Expenditures per Capita (0.880). Total Health Expenditures (0.273) made the highest contribution to the second canonical variable. Per Capita Health Expenditures (-0.315) made the highest contribution to the third canonical variable.

4. CONCLUSION

In the study, the causal relationship between death rates and socio-economic indicators is investigated. More than one dependent and more than one independent variable is used in the article. For this reason, "canonical correlation analysis" is preferred to reveal the relationship.

When correlation analysis are examined; It is seen that there is a strong relationship between death rates and socio-economic variables (0.997, 0.856, 0.723).

According to canonical correlation analysis, The number of hospitals, the number of nurses-midwives, the number of physicians, total health expenditures and per capita health expenditures are important variables in determining mortality rate.

The most important indicators of public health are maternal mortality rate, crude death rate and infant mortality rate. In order for countries to reach the level of high-income countries, public awareness should be raised. In addition, there is a need for systemic adjustments and developments. Various policy recommendations for this are recommended below.

- Awareness studies should be carried out to increase the health awareness of the society/ individuals.
- Prenatal and postnatal care and baby-child follow-ups determined by the Ministry of Health should be carried out in a timely and effective manner.
- The effectiveness of necessary trainings in health services should be increased.
- Studies should be carried out to increase the quality of health services in the community.
- Access to health services should be facilitated.
- The number of health workers should be increased.
- Improvement of health literacy in the society should be ensured.
- Investments in the field of health should be increased.

Thanks to all these recommendations, it is predicted that there will be a decrease in death rates. In addition, recording and sharing health data will contribute to the development of the field of health by paving the way for studies in this field.

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REVIEW ARTICLE

HEALTH 4.0 AND HEALTH 4.0 TECHNOLOGY APPLICATIONS

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Abstract

Health 4.0, which has developed with Industry 4.0, has started to become extremely important in terms of the health sector and health management. Today, health institutions that do not implement Health 4.0 technology applications are lagging behind in the field of health. Now, patients who receive or want to receive health services attach importance to the technologies used by the health institutions they will receive service from and prefer health institutions that have these technologies. It would be a correct approach to talk about a customer portfolio that is aware of the existence of technologies related to health care and uses them. For this reason, in our study, Industry 4.0 and previous industrial revolutions, which contributed to the emergence of Health 4.0, were mentioned first, and then Health 4.0 and, of course, previous health revolutions related to health were continued. Then, the Health 4.0 technology applications in the Health 4.0 period, which are more used, are explained, and finally, Society 5.0, which has started to become widespread today and is foreseen to exist in the future, is explained and our study is concluded by explaining how it is already integrated into the health field.

Keywords: Industry 4.0, Health 4.0, Technology Applications, Society 5.0

1. INTRODUCTION

Today, with Industry 4.0, technological development has begun to be given importance in many areas. Healthcare is one of these areas. For this reason, the technology revolution of today, which we call Industry 4.0, has also affected the Health 4.0 revolution in the field of health. Of course, as in Industry 4.0, Health 4.0 has passed through various phases until today. These phases are Health 1.0, Health 2.0, and Health 3.0.

Of course, with Health 4.0, various Industry 4.0 applications have started to be developed and implemented in the field of health. Technological applications that emerged in the Industry 4.0 era such as artificial intelligence, cloud computing, machine learning, big data, cyber-physical systems, blockchain, and the internet of things have evolved into the field of health and started to be used in the period we define as Health 4.0.

The application of the aforementioned technologies in the field of health leads to positive developments and changes. Thus, healthcare professionals can quickly recommend diagnosis, diagnosis and treatment for patients by avoiding health-related problems thanks to the technological applications found in Health 4.0. Patients also get rid of negative conditions such as the progression of their diseases, as well as quickly regaining their health with early diagnosis, diagnosis and treatment methods.

With Health 4.0, not only early diagnosis, diagnosis and treatment, but also health-related inventions gain importance. New inventions in health are becoming an important phenomenon that will reduce human deaths and prevent the spread of diseases. In addition, with Health 4.0 technological applications, patient records are kept securely and they are used when necessary.

In addition to all these, Society 5.0, which is thought to be a transition after Industry 4.0 and whose effects are starting to be seen, also causes developments in the field of health, and it is obvious that these developments in the field of health will increase even more.

2. INDUSTRIAL REVOLUTIONS

Until today's Industry 4.0 stage, Industry 1.0, Industry 2.0 and Industry 3.0 periods were passed. Figure 1 below shows the development in the Industry 1.0, Industry 2.0, Industry 3.0 and Industry 4.0 periods..

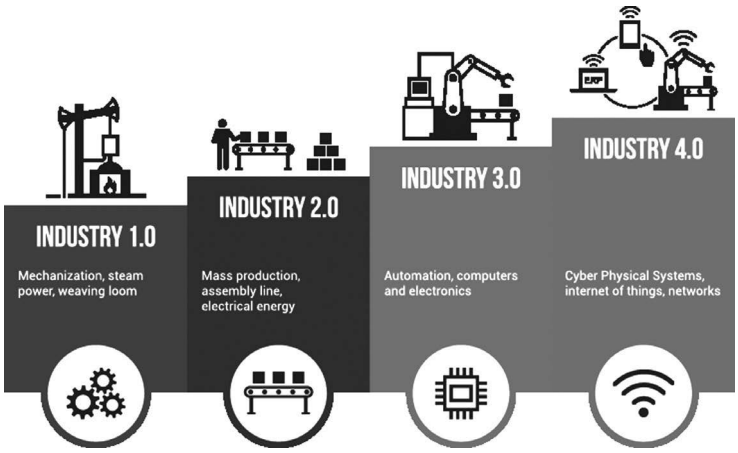

Figure 1. Industrial Revolutions (Kucera et al., 2018, 57)

1.1. Industry 1.0

With the transition of people from the communities where they make a living by hunting and gathering to the communities where they make a living by farming and stockbreeding, the transition from small settlements to urban life has begun. However, the first industrial revolution was not experienced in this period. With the invention of steam engines in the 18th century, the first industrial revolution, the Industry 1.0 period, began.

This period, in which the individuals' manual skills were required to switch to the use of machinery, included the production of chemicals and iron production, the widespread use of steam power and water power, the development of machine tools and the increase in mechanized factory systems. The first industrial revolution originated in England and then developed in Britain, North America and the Indian Subcontinent. In addition, the Industry 1.0 period started with the development and rise of trade, and continued with an improvement (Uslu, 2022, 52).

1.2. Industry 2.0

Industry 2.0, the second of the industrial revolutions, increased the division of labor and specialization with the use of electrical energy in production, thus making the transition to Industry 2.0 easier and faster. Henry Ford comes to mind when Industry 2.0 is mentioned. Ford started to use the newly found energy type electricity in production and started mass production and gained an important place in the Industry 2.0 period (Aksoy, 2017, 37).

Industry 2.0, which exists with the contribution of Fordism and Taylorism, is a period in which production with steel emerged first, and there were internal explosion engines, radio, telegraph and internal explosion engines (Şekkeli and Bakan, 2017, 19).

1.3. Industry 3.0

With Industry 3.0, machines no longer work with steam or electric power, but with computers. With the development of technology and the spread of software-supported production, the production has switched to automation system. Countries such as Japan, South Korea and China showed rapid development by coming to the fore in the Industry 3.0 period (Gökten, 2018, 882).

In the Industry 3.0 period, with the development of semiconductors, microprocessors, transistors, computers and the internet, which are also in the electronics class, progress and communication gained a new momentum (Tunçel et al., 2017, 155).

1.4. Industry 4.0

With Industry 4.0, the industrial revolutions in the past broke new ground and continue to develop and change today. The Industry 4.0 process is a period in which production and consumption completely change, the demands and needs of the customer come to the fore and production systems are determined accordingly. Some technologies have come to the fore in Industry 4.0. These;

Table 1. Industry 4.0 Technologies (Çirkin ve Özdağoğlu, 2021, 1538)

Endüstri 4.0`ın Temel Teknolojileri ve Uzantıları	**Açıklama**
Additive Manufacturing	The additive manufacturing system, also known as three-dimensional printing, is a system that can produce even complex products layer by layer in a short time by obtaining the part layer from the data of three-dimensional digital models, in contrast to traditional production systems such as milling and turning.
Augmented Reality	In addition to cooperating with individuals, autonomous robots not only contribute to flexibility, high quality and increased productivity in production, but also create a safe environment by performing dangerous and health-threatening jobs for the workforce.
Autonomous Robots	In addition to cooperating with individuals, autonomous robots not only contribute to flexibility, high quality and increased productivity in production, but also create a safe environment by performing dangerous and health-threatening jobs for the workforce.
Big Data and Analytics	It contributes to the storage, analysis and interpretation of high data rate, thus contributing to the determination of consumption habits by removing the profile of the customer, and it provides a benefit that will bring companies competing in today's globalizing world to the fore.
Cloud Computing	It is the provision of services related to computing through the internet, with high-speed, creative and flexible resources at an economical scale.
Cyber Physical Systems and Cyber Security	It refers to the network created by objects and systems through the internet, and the virtual environment created by simulation of objects and behaviors existing in the real world on the computer.
Horizontal and Vertical Integration	It simplifies production, increases resource efficiency and optimizes the global supply chain by cooperating with the internal and external environmental elements and tasks of the enterprise.
Internet of Things	It is the technology that enables all objects to reach the internet and interact and communicate with other devices.
Simulation	It is the creation of highly efficient and flexible production systems by imitating any system or process in real life in the same way on the computer and thus solving the problems at the same time by understanding beforehand.

2. CONCEPT OF HEALTH

Before explaining 4.0 in health management and technological applications used in the field of health, it is useful to define the concept of health.

In the past and traditional understanding, the concept of health has been perceived as the conditions in which a person has no disease and any disability, and has been defined within this framework. However, it should not be forgotten that illness and disability is an element that differs according to society and culture (Öztürk and Kıraç, 2019, 382)

Today, the concept of health is generally defined as follows: In daily life, it is the main right that the person should be careful about, not individually, but with more wishes, but which the relevant doctor can convey if a health-related treatment or opinion is to be declared, and the person is uncertain (Baloğlu, 2021, 50).

3. HEALTH 4.0

In this section, the Health 4.0 revolution, which emerged with the effect of Industry 4.0, and the health revolutions that occurred in previous periods related to health will be discussed. As in industrial revolutions, there are periodic developments in the field of health. These are Health 1.0, Health 2.0, Health 3.0 and Health 4.0. To summarize health trends briefly;

Table 2. Trends of Health (Karboub, vd., 2019, 2)

	Aim	Focus	Used Technology
Health 1.0	Increasing productivity and reducing paperwork	Automation	Computers and administrative software tools
Health 2.0	Improving data sharing and productivity	Connectivity – Network of hospitals/organizations	Cloud Computing
Health 3.0	Developing and equipping hospitals, providing hospital-based services	Communication with patients	Big data, wearables, optimization systems
Health 4.0	Value-centric service, real-time monitoring and monitoring	Prediction and diagnosis with artificial intelligence support	IoT, artificial intelligence, data analytics

Health 1.0: Health care is a stage where more doctors are centrally located. In Health 1.0, health care coincides with the first stage of technology. Patient records were made manually and services were provided with simple tools.

Health 2.0: The provision of health services has begun to be created in electronic environment with the method of simple networks. The registration procedures of the patients were also recorded with this system. Recording in the electronic environment has become a method preferred by healthcare professionals in order to communicate more healthily with patients.

Health 3.0: It has been a period when computers and digitalization became more concentrated and used. Obtaining data with the help of technology by collecting information is one of the main purposes. Genetic information has been used and wearable devices have developed. It is a stage in which sick people give information to other people through social media. This is called "Digital Healing" (Yalman and Filiz, 2022, 55-56).

Health 4.0 is defined as "a strategic concept for the healthcare field derived from the Industry 4.0 concept". The term is often used synonymously with digital health, m-health, e-health, and smart health. Behind this concept is the goal of virtualization in healthcare and personalization for patients, professionals and other stakeholders and the overall improvement of the technology and healthcare industry. In short, Health 4.0 can be defined as the phenomenon of improving health care and improving the connection between health care stakeholders using technology. As the main stakeholder of the digitally connected health system, the development of Health 4.0 technology, primarily meeting patient needs and improving the service received by patients, is at the center of this technology. To achieve this, the patient should receive the best possible and timely medical care when he needs it. This demand has led to the struggle for personalization of health with completely personalized services that offer the most benefit to patients (Bause et al., 2019, 888-889).

Health 4.0 provides a structural, behavioral and cultural transformation of health services by bringing virtuality and digitalization in the design and delivery of health services. The literature has understood Health 4.0 as the application of "Industry 4.0" principles to health care. More specifically, Health 4.0 requires "…a tactical deployment and management model for healthcare inspired by Industry 4.0". It aims to smarten the functioning of healthcare organizations by recontextualizing the delivery of healthcare services in the cyber-physical environment. Making this progress requires leveraging the potential of modern technologies such as artificial intelligence, machine learning and big data analytics (Ciasullo, 2022, 1).

3.1. Health 4.0 Technology Applications

The scope of Health 4.0 is quite broad. However, common Industry 4.0 applications used in Health 4.0 are listed as follows:

3.1.1. Use of Artificial Intelligence in Healthcare

Artificial intelligence can be defined as the imitation of human intelligence by "intelligent" machines that can make decisions autonomously and perform many different tasks that normally require humans. It is widely used in many fields for data structuring, feature extraction, classification and prediction. State-of-the-art technology offers different use cases in healthcare. Artificial intelligence can be used in the field of health for the following purposes:

- Monitoring the patient and providing accurate early warning for critical diseases such as cardiovascular diseases,

- Real-time decision making and assistance,
- Maximizing positive/negative predictive values,
- To accelerate obtaining primary diagnoses according to their urgency (Karboub et al., 2019, 3).

In addition, artificial intelligence is to help people stay healthy. Thus, they do not need a doctor or this need will decrease to a minimum after a while. The second application area is its use for both early diagnosis and diagnosis. With IBM's Watson for Heath application, it is very easy to access health data. Another application is treatment. It contributes to the detection and treatment of people with chronic diseases. It also contributes to research, especially helping the discovery of drugs. Artificial intelligence is used by doctors to decide which treatments they should apply. Another important artificial intelligence application is elderly care. It can perform elderly care in a way that reduces the use of hospitals and nursing homes. In addition, medical students can benefit from artificial intelligence in education (Büyükgöze and Dereli, 2019, 2-3).

3.1.2. Use of Cloud Computing in Healthcare

Cloud computing is a horizontal innovation consisting of a three-tier eHealth architecture designed to process data from ingestion to the cloud.

Medical Device Layer: This layer is where data is collected using different IoT. Strengthens the health 4.0 capacity to monitor patients in real time. This layer offers the advantage of being low cost and error free. Therefore, it generates sensitive and large amounts of data that must be handled with care.

Fog Layer: Equipped with high technology connected with different types of sensors. This subsection of sensor groups helps to process the incoming data in a very short time. After the data is processed, it is sent to the Cloud Tier for further analysis.

Cloud Layer: In this last layer, the cloud equipped with different high-performance computers can perform different highly specific tasks. The received data is also analyzed, stored and made available for further access by patients and authorized hospital staff. This layer allows both dynamic decision making and patient historical data (Karboub et al., 2019, 2-3).

3.1.3. Use of Blockchain in Healthcare

Healthcare always requires the collection, storage and use of sensitive data and classified information. They also require reliable operations and policies and adequate knowledge to ensure control and compliance. In addition, as healthcare systems expand to include multiple institutions or organizations along the value chain, reliable and secure methods of establishing contracts and agreements are required. Blockchain is one of the important and effective technologies for providing these services. With blockchain, secure and unalterable records can be stored and used for verification and security. Non-repudiation and transparency also ensure reliable contracts and clear agreements on cooperation

rules and procedures. It can also provide mechanisms to ensure fairness in data sharing and protect patients' privacy (Al-Jaroodi et al., 2020, 211191).

3.1.4. Use of Internet of Things in Healthcare

Lack of knowledge about a health problem and corresponding appropriate management can aggravate conditions and result in high mortality rates. Successful application of IoT in disease management and health education are key issues. With IoT and 5G, all kinds of multimedia material related to disease education can be sent to patients' mobile terminals, increasing their knowledge about their condition while integrating pharmacological and non-pharmaceutical treatments. In addition, IoT facilitates the assessment and monitoring of diseases. For example, patients can habitually check their tests and surveys using their mobile phones, so doctors can regularly monitor their patients' condition. Alternatively, healthcare professionals, decision makers and service providers can apply IoT to evaluate conditions dynamically and how they interact with environmental or behavioral aspects (Monteiro et al., 2018, 270).

3.1.5. Use of Big Data Analytics in Healthcare

A large amount of data accumulates in health systems over time. These become inputs for decision making and future planning practices. Big data analytics offers advanced mechanisms to discover health trends, correlations, and insights from this data. This helps improve healthcare, systems and treatment procedures; it reduces health costs, improves the quality of health services and facilitates decision-making for public health, and provides information to develop personalized treatments for individuals (Al-Jaroodi et al., 2020, 211191).

3.1.6. Use of Medical Cyber-Physical Systems (Medical CPS)

Medical CPS is used to facilitate beneficial interactions between the cyber world (eg software and control signals) and the physical world (eg equipment and patients) by providing ongoing health monitoring and treatment services. Medical CPS uses built-in feedback controls to accurately monitor and react to specific conditions. Examples of medical CPS are implantable medical devices (IMDs), such as deep brain simulators used to treat epilepsy, pacemakers used to regulate heart rate, and bio-instruments used to deal with biosignals (Al-Jaroodi). et al., 2020, 211191).

3.1.7. Machine Learning in Healthcare

Machine learning in health services is applied to provide high quality health services to patients in order to save both work and time to predict, diagnose and determine complications after the disease (Veranyurt et al., 2020, 278).

In addition, while obtaining medical data with machine learning, it is also possible to analyze and reach results quickly. As a result, rapid decision making, increased efficiency and clinical trials are being developed. While costs are reduced with machine learning in health, personalized treatments can be

determined and patient appointment planning is facilitated. Applications made with machine learning in the field of health are as follows:

- Identification of the disease and diagnosis of the disease,
- Personalized treatment, behavioral modification,
- Pharmaceutical invention and production
- Clinical research
- Radiotherapy and Radiology
- Smart Electronic Health Records
- Forecasting the epidemic (Kamer and Sancar, 2022, 18-19).

4. SOCIETY 5.0 AND ITS INTEGRATION IN HEALTH

Today, the period following Industry 4.0 has begun to be called and defined as Society 5.0. In addition, Industry 4.0 has affected the technological developments in the field of health, and Society 5.0 has started to direct the technological developments in the field of health, and it is foreseen that this orientation will also exist in the future. First of all, it is useful to explain Society 5.0.

Industry 4.0 was pioneered by Germany, while Society 5.0 was pioneered by the Japanese prime minister, who attended the CeeBIT Informatics Fair in 2017. He initiated Society 5.0 in Tokyo by defining Society 5.0 as technology should be understood as a help, not a threat to societies. The main purpose of Society 5.0 is to integrate technological developments and changes with society. In this way, technology will live in coordination with society (Saracel and Aksoy, 2019, 29).

In addition, Society 5.0 will help people develop a global perspective quickly, by changing the structures of institutions, organizations, professions, and blending them with technological developments. The individual, who will benefit more from machines in the coming years, will become more machine-dependent than before and will increase the expectation of a high quality life standard in people over time (Karoğlu et al., 2020, 148).

In addition to these, it is useful to refer to the United Nations' sustainable development goals in order to see the effects of Society 5.0 on health practices more clearly. According to Figure 2., the UN's sustainable development goals are as follows:

Health and quality life, which is the third of the 17 goals of sustainable development of the United Nations in Figure 2., includes health practices in Society 5.0. These are in health;

- Wearable health applications,

- Mobile health applications,

- Artificial intelligence applications. Thus, people will be able to manage their personal health (Büyükgöze and Dereli, 2020, 2-3).

Figure 2. Sustainable Development Goals **(**https://www.un.org/development/desa/disabilities/about-us/sustainable-development-goals-sdgs-and-disability.html Retrieved From: 15.11.2022)

5. CONCLUSION

Technological developments continue to exist and increase in the field of health. In this case, the important point is that health institutions should follow the technological changes and developments in both Industry 4.0 and Society 5.0. Today, when patients want to receive health services, they choose and will continue to choose health institutions that are technologically competent.

In addition to all these; health institutions must follow the technological developments and must not lag behind these developments. Thus, they will be able to keep up with the necessary competitive conditions. They will also provide a good health service with the application of technological developments.

Apart from these, new inventions will be made thanks to health-related technologies, and diseases and epidemics will be prevented. As a result, technologies applied in health are becoming increasingly important. These developments, which are related to human life, will benefit humanity. In fact, it is predicted that people will self-medicate with health technologies in the future.

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