MEDICAL AND HEALTH SCIENCES

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CONTENTS

FOREWORD

With the latest technological developments in the field of health and medicine, the interest in research on the development of novel methods for the diagnosis and treatment of diseases and the development of preventive health services has increased. Experts from different disciplines to identify common intersections for the solution of an existing problem, and experts working in each discipline to come up with appropriate solutions; and the fact that these experts act with the understanding of preventing diseases and sustainable health increases human health and quality of life.

Multidisciplinary studies aimed at the comprehensive research and application of current issues in the fields of Medicine and Health Sciences are of importance. This book aims to introduce studies from disciplines related to Medicine and Health Sciences into the health sciences literature. I would like to thank the authors who contributed to the creation of this book and the reviewers who contributed to the evaluation of the studies. I wish success in all their studies that will contribute to the literature in the future.

Assist. Prof. Dr. Seyhan ÇANKAYA

CHAPTER 1

ANALYSIS OF THE INFORMATION CONTENT AND READABILITY OF TURKISH WEB PAGES RELATED WITH COVID-19

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INTRODUCTION

The internet, which provides the opportunity to adapt to the rapidly developing world and learn correct information more quickly, is an indispensable element in the life of today's people (Kozanhan & Tutar, 2017). According to the data of Digital 2019, the rate of internet use is 72% in Turkey (Datareportal, 2019). The main purposes for the emergence of the internet include facilitating information and accessing information easily, cheaply, quickly and safely. It has been reported that the increase in the use of computer and smart phones has caused the internet to spread much faster than estimated (Arısoy, 2009). There was a 9% increase in the rate of internet users in 2019 when compared with the year before. It has been reported that individuals spend an average of 7 hours a day on the internet and that the rate of smart phone use is 77% (Datareportal, 2019). With the internet becoming more widespread, a large number of individuals refer to the information pages on the internet for health-related decisions (Kozanhan & Tutar, 2017). According to TÜİK 2016 data, the frequency of searching health information on the internet for any reason is 65.9%. In a study conducted by Beck et al., it was reported that 48.5% of the individuals used the internet to access health information and that they found the information on websites accurate and reliable (Beck et al., 2014). In a study conducted on elderly individuals, it was found that while 43.8% of the participants used the internet to access health information the most; television, newspapers and health magazines ranked the second in the search of information (Medlock et al., 2015). In another study conducted, it was found that

more than half of the individuals who reported that they used the internet in the field of health used the information they obtained from these websites to make medical decisions (Fox & Jones, 2009).

Patient information texts presented on the internet can be used to help patients by explaining the indications, benefits and possible risks of medical practices (Strachan et al., 2012). In a study conducted, it was found that the individuals used the internet most frequently to get information about the symptoms they experience, the course of their disease, treatment options, to obtain additional information about drugs and about how to deal with the side effects and to get information about practical care and nutrition/exercise (Medlock et al., 2015). In a different study, it was found that getting health information through the internet was beneficial in individuals' evaluating their health and managing health-related problems (Ahmad, Hudak, Bercovitz, Hollenberg, & Levinson, 2006). In addition, it has been shown that patient information texts can be effective in solving health problems with their benefits such as providing communication between the patient and healthcare personnel and facilitating the compliance of the patient to the treatment (Ritterband, Thorndike, Cox, Kovatchev, & Gonder-Frederick, 2009). However, since the value of information is limited with the ability of patients to comprehend this, the "readability" and "understandability" of this information on the internet is as important as reliability and up-to-datedness (Finnie, Felder, Linder, & Mullen, 2010).

Readability is defined as the texts' being easy or difficult to comprehend by the readers and it is reported as an objectively measurable concept (Eker, Tüzün, Aytar, & Daşkapan, 2013). According to the studies conducted on the relationship between readability and the ability to understand, it has been found that the comprehension rate of the reader increased as the suitability of the text to the reader's level increased. In other words, there is a linear relationship between reading level and comprehension level (DuBay, 2004; Wang, Miller, Schmitt, & Wen, 2013). While a text's being difficult makes reading difficult, its being easy reduces the interest in reading. For these reasons, training materials should be prepared taking into account the characteristics of the target group (Huang et al., 2015).

The main criteria used in evaluations made in terms of texts' being easy or difficult to understand are parameters such as sentence length, word length, and number of syllables in the word. Concrete-abstract words, compound-simple words, affixes and phrases can also be listed in addition to these three parameters (Boztaş et al., 2014). With these parameters, many different proportional values/readability formulas have been developed by researchers. By using these formulas developed, the level of education required to comprehend the information in the text is described (DuBay, 2004). Fry Readability Formula, Flesch–Kincaid Readability Formula, Flesch Reading Ease Test (FRES), Simple Measure of Gobbledygook (SMOG), Gunning Fog index and Dale Cale formula are some of the frequently used

international tools. Ateşman readability formula and Bezirci–Yılmaz readability formula are formulas designed to find out the readability levels of Turkish texts (Orgun & Akkoç, 2020). The American National Institute of Health recommends complex medical information to be written in an effective way to maximize comprehension and in a way suitable for a six-year long or less level of education since approximately 40% of American population have insufficient health literacy (Finnie et al., 2010). The American National Institute of Health, American Medical Association (Walsh & Volsko, 2008) and U.S. Department of Health and Human Services (U.S. Department of Health and Human Services, 2010) recommend patient information materials to be written at 4th and 6th grade reading level; while Centers for Disease Control Prevention recommended readability to be lower than 8th grade reading level (Centers for Disease Control Prevention, 2018). Studies conducted show that if the content of information exceeds an average reading level of 7th grade, it will not be very possible for consumers to understand (Walsh & Volsko, 2008).

The present age, which is called the information age, provides easy access to information thanks to the internet, while at the same time it has prepared the ground for the formation of information stacks. Considering that there are about 500 million websites, it will be easier to understand the level of information pollution. In the process of reaching information through the internet, the masses that turn into

user and participation from audience-listener begin to prefer stacks of information the sources of which are unknown (Yüksel, 2014).

COVID-19, which has spread to all continents except Antarctica since its appearance in late 2019, is a health crisis that reveals the contemporary situation of the world in 21st century. While this health crisis continues, states all around the world are fighting with all their power to slow down the spread of the disease by taking various economic, social and political measures (UNDP Turkey, 2020). As a result of the restricted freedom of individuals during COVID-19 pandemic days, and due to fear of being sick and losing the loved ones, health anxiety levels increase (Tutku, Iliman, & Dönmez, 2020). During the pandemic, various kinds of information have been included on the web pages designed to inform the society about COVID-19. However, in order for informative texts on web pages to be beneficial to individuals, they should be prepared at a level appropriate to the education level of the readers. Since the value of information is limited to the ability of readers to comprehend it, the readability and understandability of this information on the internet is very important (Deniz, Kozanhan, Tutar, & Özler, 2020). In the light of all this information, it is important for healthcare personnel who are obligated to provide health education to society to follow these developments and to be aware of how individuals can benefit from the web environment. It is thought that examining the websites that provide health information to the society will be beneficial especially during this period of COVID-19 pandemic. The present study was conducted

to examine the information content quality and readability of Turkish web pages related with COVID-19.

1. METHOD

In this descriptive study, the first 100 websites accessed in the search conducted in May 2020 by using the key words “COVID-19”, “COVID-19 and disease”, “COVID-19 and treatment” in the Google search engine were evaluated. Commercial blog sites, sites including ads, sites including only pictures or videos, chat sites, forum sites, magazine sites, sites which were not informing the society and sites with less than 100 words were excluded from the study. The sample of the study consisted of 38 websites. Information content of the web pages was evaluated with Quality of Criteria for Consumer Health Information (DISCERN) measurement instrument, readability levels were evaluated with Flesch Reading Ease Test (FRES), Ateşman readability formula and Bezirci–Yılmaz readability formula.

1.1. Quality of Criteria for Consumer Health Information (DISCERN)

DISCERN was developed by Charnock et al. (1999) to evaluate the content and quality of education material. Turkish validity and reliability study of DISCERN was conducted by Gökdoğan (2003). DISCERN includes 16 questions about the content of the material. While the first part consisting of eight questions evaluates the reliability of the material, the second part consisting of seven

questions measures the quality of the information provided about the treatment/care options and the third part consisting of one question makes an overall evaluation of the material. In DISCERN, each question is scored from 1 to 5 and "5" indicates the appropriateness of the material, while "1" indicates its inappropriateness. By adding the responses to each item, a score between 15 and 75 is obtained. Item 16 which gives the overall evaluation is evaluated separately. A low score in the evaluation shows poor quality, while a high score shows good quality.

1.2. Readability Measurement

Information texts in the websites included in the research were transferred to Microsoft Word program separately and author information, titles, website URLs and links were removed to prevent readability evaluation results from being affected. The texts edited in Microsoft Word were transferred to computer software program developed by Bezirci-Yılmaz. The data transferred to software program were used in the calculation of readability values of FRES, Ateşman and Bezirci-Yılmaz formulas.

Flesch Reading Ease Test (FRES) was published in 1948 by Flesch. The readability test gives numerical data about how easily readable and understandable the prepared content is and which age groups can understand it easier. For example, in Flesch Reading Ease Test, a paragraph of 100 words is chosen, total number of words, syllables and sentences is calculated and reading ease score is calculated according to the following formula.

Flesch Reading Ease Formula= 206.835 - 1.015 x (number of words/number of sentences) + 84.6 x (number of syllables/number of words)

A high score found with this test shows that the prepared content can be read easily, while a low score shows that the content is difficult to understand. The FRES score obtained can be converted into an approximate level of education. In FRES formula, if the readability score of a text is between 90 and 100, it is defined as “very easy” at 5th grade level; if it is between 80 and 89, it is defined as “easy” at 6th grade level; if it is between 70 and 79, it is defined as “fairly easy” at 7th grade level; if it is between 60 and 69, it is defined as “standard” at 8th-9th grade level; if it is between 50 and 59, it is defined as “fairly difficult” at 10th-12th grade level; if it is between 30 and 49, it is defined as “difficult” at university level and if it is between 0 and 29, it is defined as “very confusing” at university graduate level (The Flesch Reading Ease Readability Formula http://www.readability formulas.com/flesch-reading-ease-readability-formula.php) .

Ateşman Readability Formula, which was defined by Ateşman in 1997, was developed with the adaptation of Flesch Reading Ease formula based on the length of words and sentences.

Readability score= 198.825-40.175 x (total number of syllables/total number of words)- 2.610 x (total number of words/total number of sentences).

In Ateşman formula, the readability of the text is defined as “very easy” when the score is between 90 and 100, as “easy” when the score is between 70 and 89, as “moderate” when the score is between 50 and 69, as “difficult” when the score is between 30 and 49 and “very difficult” when the score is between 1 and 29 (Ateşman, 1997).

Bezirci Yılmaz Readability Formula ; Bezirci Yılmaz Readability Formula was developed in 2010 based on the characteristics of different readability formulas developed so far and the statistical characteristics of Turkish. Two features are especially emphasized in the use of this new formula. The first of these features is average sentence lengths, while the second is the number of syllables. The number of words in sentences affects the readability of that text.

$$\sqrt{OKS \times ((H3 \times 0{,}84) + (H4 \times 1{,}5) + (H5 \times 3{,}5) + (H6 \times 26{,}25))}$$

OKS: Average number of words

H3: Average number of words with 3 syllables

H4: Average number of words with 4 syllables

H5: Average number of words with 5 syllables

H6: Average number of 6 or more words

According to this formula, readability level of texts decrease as the number of words in sentences decrease in texts. Similarly, the increase in word length also makes the readability of words and sentences more difficult. The readability score from this formula corresponds to

grades in Turkish education system. Level of education shows "primary education" for grades 1-8; "secondary education (high school) for grades 9-12; "university" for grades 12-16 and "academic education" level for grades 16 and higher (Bezirci & Yılmaz, 2010).

Data Analysis

Descriptive statistics of the categorical data in the study were shown by using frequency and percentage values, while numerical data were shown by using averages and standard deviation. SPSS 25.00 (IBM Inc, USA) software was used for data analysis.

2. RESULTS

38 web pages which met the inclusion criteria were evaluated. No application was found on any of the web pages where users could interact and make suggestions.

The quality of information, reliability and general evaluation of the content of web pages were evaluated by using DISCERN measurement instrument. Table 1 includes each item of DISCERN, score averages of websites and standard deviations. The first, second, third and sixth questions in the first part of the measurement instrument which evaluated the reliability of web pages had the highest average. In the second part in which the quality of the content of web page was evaluated, question 15 was found to have the highest score average. The average of the third part in which the overall

quality of the web page was evaluated was found as 3.1±0.7 out of 5 (Table 1).

Table 1. DISCERN score averages of Websites

	Ave±sd
PART 1	
1. Is the purpose of the Web page clear?	4.8±0.4
2. Can these purposes be achieved?	4.7±0.5
3. Is the Web page relevant with the subject?	4.9±0.1
4. Are the resources used in the preparation of Web page clearly stated?	1.7±1.3
5. Is the date of the information reported or used on the website clearly stated?	2.4±1.9
6. Is the information provided on the website consistent and unbiased?	4.9±0.1
7. Does the Web page give details about additional information or support resources?	1.5±1.1
8. Does the Web page mention any ambiguous aspects?	2.7±1.2
PART 2	
9. Is it described how each treatment is applied?	2.5±1.3
10. Does it describe the benefits of each treatment?	1.5±0.9
11. Does it describe the risks of each treatment?	1.2±0.5
12. Does it describe what will happen if treatment is not given?	1.4±0.8
13. Does it describe how treatment options affect quality of life?	1.4±0.8
14. Is it explained that there may be more than one treatment options?	2.1±1.2
15. Does it provide support for the patient to decide?	3.1±1.0
PART 3	
16. What is the overall evaluation of the web page?	3.1±0.7

Table 2 includes the score averages of DISCERN measurement instrument and its sub-dimensions. It was found that average score taken from the first part of DISCERN measurement instrument (reliability of the material-8 items) was 28.0±3.8, while the average score taken from the second part (treatment/care options) was 13.5±5.1 and the average score taken from the third part in which the overall quality of the web page was evaluated was 3.18±0.7. Total average score of the websites according to DISCERN measurement instrument was 41.5±7.35.

Table 2. Score averages of DISCERN Measurement Instrument and Sub-scores

DISCERN Score	Score range	Ave±sd
Items 1-8	8-40	28.0±3.8
Items 9-15	7-35	13.5±5.1
Items 16	1-5	3.18±0.7
Total Score	15-75	41.5±7.35

Readability average of all websites in the study was found as 24.54±4.7 “very difficult” and at university graduate level according to FRES readability value; as 53.27±9.3 and “fairly difficult” according to Ateşman’ readability value. Bezirci-Yılmaz’s readability value was found as 14.35±3.05 at university level.

3. DISCUSSION

The results obtained as a result of the analysis of research data were discussed in the light of the related literature.

In the web pages evaluated in the study, no applications were found where users could interact and make suggestions. In a study conducted by Moick and Terlutter (2012), it was shown that with the use of the internet for communicating with patients, control visits of patients decreased, chronic disease management improved and the attitudes of patients and physicians for online communication changed positively. Laugesen et al. (2015) showed that when the physician was consulted through the internet, patients' fears decreased, adaptation to the proposed treatment program improved and the consultancy given through the internet closed the information gap between the physician and the patient.

Online communication opportunity on web pages will enable individuals to access more reliable information about health.

In the first part of our study in which the reliability of the material was evaluated according to DISCERN measurement instrument, score average was found as 28.0±3.8; in the second part in which treatment/care options were evaluated, score average was found as 13.5±5.1 and in the third part in which the overall quality of the web page was evaluated, score average was found as 3.18±0.7. In a study in which the quality of web pages developed about childhood epilepsy was analysed by using DISCERN measurement instrument, 50

websites were reached and it was found that only 9.6% of these websites had good reliability, 7.2% had good quality information about treatment options and 21.5% had good quality of content (Cerminara, Santarone, Casarelli, Curatolo, & El Malhany, 2014).

In our study, total score of the websites according to DISCERN measurement instrument results was found as 41.5±7.35. In DISCERN measurement instrument, total score being 40 and higher shows that the content of the material developed is good (Tirlapur, Leiu, & Khan, 2013). According to this result, it can be seen that the information quality, content and reliability of the website is high. In their study which evaluated the usability of 22 websites developed about childhood asthma, Banasiak and Meadows-Oliver (2017) used the 6-item short version of DISCERN measurement instrument in which the total score ranged between 6 and 30. As a result of this, it was found that the average score of the websites evaluated was 17.32±6.71. In their study which evaluated the quality of web pages developed for informing patients about tonsillectomy and sleep apnoea by using DISCERN measurement instrument, Chi et al. (2017) found that the average score of websites was 60.5±12.3. In a study in which 421 websites about systemic lupus erythematous were evaluated in terms of quality, reliability and readability, it was found that DISCERN score ranged between 19 and 75 and average score was 47.7±13.2 (Reynolds, Hoi, & Buchanan, 2018). The results of the study are similar to the results in literature.

In our study, it was found that readability value was 24.54±4.7 at "very difficult" level and at a level university graduates could understand according to Flesch Reading Ease (FRES) formula. In their study they evaluated the online patient training materials of ophthalmology associations, Huang et al. (2015) found readability value as 40.7 according to FRES formula; in their study they evaluated the readability of internet based patient training materials for parathyroid surgery, Patel et al. (2015) found readability value as 42.8± 16.3 according to FRES formula; in their study they evaluated the readability of internet based patient training materials for endoscopic sinus surgery, Cherla et al. (2012) found readability value as 47.1±13.4, at "difficult" and university level according to FRES formula. In their study, Banasiak and Meadows-Oliver (2017) found readability value as 53.57±15.03, at 10-12th grade level and as "fairly difficult" according to FRES formula. Although the study results are different from the literature, it was found that the websites examined were found to be in higher levels than the recommended education level.

In our study, Ateşman's readability value was found as 53.27±9.3 and at "fairly difficult" level. In their study they evaluated the readability of patient information texts provided in internet websites in the field of anaesthesiology, Kozahan and Tutar (2017) found Ateşman readability value as 48,9 (45,2-53,1) for spinal and epidural anaesthesia and as 42,9 (38,9-48,6) for general anaesthesia. According to this result, average readability range was found as "difficult" for

both anaesthesia types. In their study they evaluated the readability of informed consent forms used for emergency procedures, Sönmez et al. (2018) found Ateşman readability value as 62.7±9.8 and at “fairly difficult” level. In their study they evaluated the readability of patient training materials about breast cancer, Aksoy et al. (2019) the readability of websites as “fairly difficult” according to Ateşman readability formula. In a study in which the readability of online texts about autism spectrum disorder was evaluated, Kara (2019) found readability value as 43.72±1.45 and at “difficult” level according to Ateşman readability formula. In their study they evaluated the readability and content of patient information texts related with lymphedema published on internet websites, Tolu and Basım (2018) found readability value of websites as 58.81±10.88 and at “fairly difficult” level according to Ateşman readability formula. In their study they evaluated the readability of intravenous and intramuscular injection approved consent forms, Ebem et al. (2019) found readability value of all consent forms as 56 (50–60) and as “fairly difficult” according to Ateşman readability formula. In their study they evaluated the readability of Turkish internet websites about substance abuse, Çifci et al. found readability value as 46,03±11,67 and at “difficult” level. In their study they evaluated the readability and content of internet information texts about triple test, Deniz et al. (2020) found readability value as 57.6 (53.9-61.9) and at “fairly difficult” level according to Ateşman readability formula. In their study they evaluated the readability of pre-anaesthesia existing informed consent forms, Boztaş et al. (2014) found Ateşman

readability value as 33.2 (26.0-37.0) and at “difficult” level. The result of the study was found to be similar with the literature.

In our study, Bezirci-Yılmaz’s readability value was found as 14.35±3.05 at university level. In Kozahan and Tutar’s (2017) study, Bezirci-Yılmaz readability value was found as 15,0 (12,7-15,9) for general anaesthesia and as 12,5 (11,3-14,0) for spinal and epidural anaesthesia. With this formula, it was found that the texts prepared for both anaesthesia types required “university graduate” education level according to the education system of our country. In Sönmez et al.’s (2018) study, Bezirci-Yılmaz readability value was found as 10 ± 1.12 at “high school” level. In Aksoy et al.’s (2019) study, “secondary (high school)” level was found according to Bezirci-Yılmaz readability formula. In Kara’s study (2019), Bezirci-Yılmaz readability value was found as 14.68 ± 0, 52 requiring “university graduate” education level. In Tolu and Basım’s (2018) study, Bezirci-Yılmaz readability value was 11.47 ± 3,48 at “secondary (high school)” level. In Ebem et al.’s study readability value of all consent forms was found as 2,93 (2,85–2,99) at “secondary (high school)” level according to Bezirci-Yılmaz readability formula. In Çifci et al.’s study (2020) Bezirci-Yılmaz readability value was found as 14,04±4,12 at “university graduate” level. In Deniz et al.’s study (2020) Bezirci-Yılmaz readability value was found as 12.27 (10.83-13.90) at “university graduate” level. Although study results were found to be different from the literature, it was found that the websites

examined were found to be in higher levels than the recommended education level.

4. CONCLUSION

It was found that web pages had moderate level of quality and their readability was difficult at a level individuals with university education level could understand. It was found that the readability level of websites related with COVID-19 were much higher than the recommended level. Providing information with clear, understandable and appropriate reading level will contribute to the development of communication between healthcare professionals and individuals. It is recommended to revise the existing information texts according to readability criteria and to develop new texts which the general population will understand.

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CHAPTER 2

AN EVALUATION OF COVID RELATED CLINICAL TRIALS IN WORLD AND TURKEY

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INTRODUCTION

COVID-19 is a new disease caused by coronaviruses (WHO, 2020a). It is different from other diseases, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS); the virus spreads rapidly, and outbreaks can grow at an exponential rate (WHO, 2020b). The COVID-19 pandemic, or coronavirus pandemic, virus outbreak that occurred in Wuhan, the capital of China's Hubei region on December 1, 2019 (www.bjnews.com.).

A new coronavirus, called SARS-CoV-2 (Fox, 2020), was diagnosed when a pneumonia that developed for no specific reason in various patients and did not respond to vaccines by treatment. The transmission rate of the virus that can be transmitted from person to person grew in mid-January 2020 (CNBC.2020; The Washington Post, 2020). Then virus cases in various countries in Europe, North America and Asia-Pacific started to be reported (www.cdc.gov). Global epidemic was declared by the World Health Organization on March 11, 2020 (www.cdc.gov).

Coronavirus (COVID - 19) pandemic had a devastating effect on people's daily lives, causing stagnation and shrinkage in the country's economies. The characteristic features of COVID-19 epidemic that are effective in turning into a pandemic in a short time are discussed under three main headings in the literature. These headings are;

- *Speed and scale:* Covid-19 diseases caracteristic is to spread quickly around the world, and caused serious intensity on health systems.
- *Severity:* showed severe / critical effects in 20% of total cases. Covid-19 related deaths rate was currently over 3% and this rate increases in the elderly and those with certain underlying diseases.
- *Societal and economic disruption:* Covid-19 disease effects health and social care systems with shocks and caused deep at the socio-economic outcomes (WHO, 2020b).

In this context, countries have started to form the programs for fighting against pandemic immediately. The world health organization had determined a number of strategies to manage/control the coronavirus pandemic and had prepared guidelines to guide countries to implement these strategies. "Covıd-19 Strategy Update" was prepared by WHO. In this guideline the global strategic objectives are as follows:

- Countries mobilize to ensure that every segment of the society takes individual measures (hand hygiene, respiratory etiquette and physical removal at the individual level)
- Controlling, quarantining and supporting individual of cases that are infrequent or in a cluster, must be provided application of isolation by fast detection of cases, and proper care of persons
- Suppress community communication through population-level physical removal measures, infection prevention and control

measures, and restrictions suitable for non-mandatory domestic and international travel

- Reduce mortality by maintaining unprotected populations by ensuring appropriate clinical care for cases affected by COVID-19, ensuring continuity of primary health and social services by protecting employees in the system
- To develop safe and effective therapeutics and vaccines that are easy to access according to need (WHO, 2020b).

With these strategies, each country makes arrangements to implement a comprehensive set of measures in line with their capacities to slow down COVID-19-related deaths and reduce mortality. According to data from countries affected in the pandemic, it is expected that Covid-19 disease effects about 40% of cases will experience mild, 40% will experience moderate including pneumonia, 15% of cases will experience severe and 5% of cases will have critical disease (WHO, 2020b).

As of June 22, 2020; while the number of 8,860,331 confirmed cases; the number of 465,740 patients died due to the corona virus globally.

Table 1: Covid-19 Related Cases-Deaths (by WHO Region), 06/22/2020[1]

	Cases	Deaths
Globally	**8,860,331**	**465,740**
Africa	224,673	4,996
Americas	4,370,519	221,771
Eastern Mediterranean	914,518	20,531
Europe	2,543,778	193,366
South-East Asia	600,191	17,734
Western Pacific	205,911	7,329

Source: Coronavirus disease (COVID-19) Situation Report – 154, WHO, 2020

The distribution of Covid-19 cases according to region was evaluated in that respectively; Americas (49%), Europe (29%), Eastern Mediterranean (10%), South- East Asia (7%), Africa (3%) Western Pasific (2%).

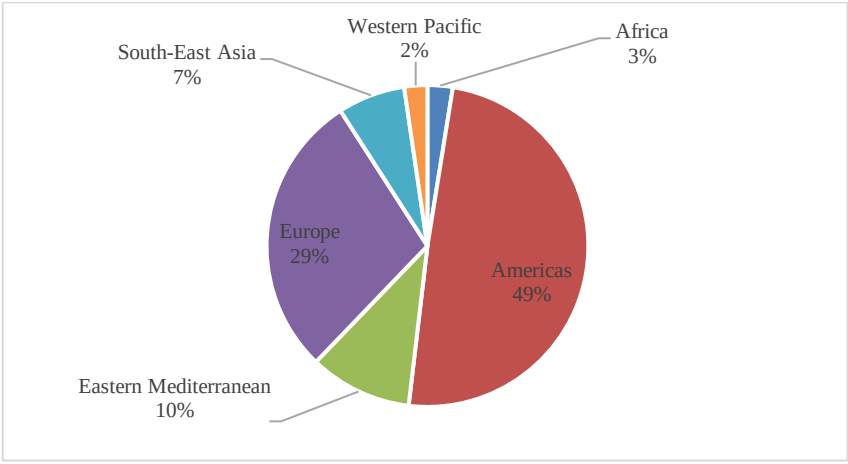

Chart 1: COVID-19 Related Cases, World, 22 June 2020

[1] See Annex 1 to detailed information about the countries, territories or areas with reported laboratory-confirmed COVID-19 cases and deaths, by WHO region .

The distribution of Covid-19 related deaths according to region was evaluated in that respectively; Americas (48%), Europe (41%), Eastern Mediterranean (4%), South- East Asia (4%), Western Pasific (2%), Africa (1%).

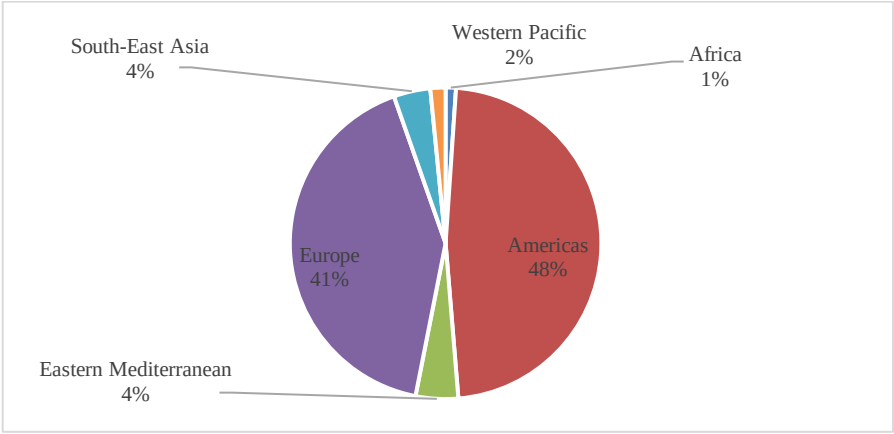

Chart 2: COVID-19 Related Deaths, World, 22 June 2020

To prevail against COVID-19, everyone (every country, every sector, every people) has playing a crucial role to stop COVID-19 disease. According to "Global research and innovation forum: towards a research roadmap"; the global strategıc approaches and critical actions were proposed with eight items as follows:

- Mobilize research on rapid point-of-care diagnosis for community-level use - this is important for quickly identifying, treating sick people and better predicting how far the virus has spread.
- Rapid evaluation of available country data to achieve the most effective standard care approach to patients - optimizing the

standard of care provided in different processes of the disease, utilizing all available technological innovations to ensure survival and improvement.

- Evaluate the effect of adjunctive and supportive therapies as fast as possible - the global research community needs to understand that we are using other adjunctive treatments (including a rapid assessment of interventions such as steroids and high flow oxygen) that can assist the standard of care provided to patients.
- Optimize to use of personal protective equipment and other infection prevention and control measures in health care and community settings – it is crucial to preserve health care workers and the community from contamination and create a safe working surroundings
- Review of available evidence to identify animal host (s), prevent continuous shedding, and better understand virus infectivity, disease severity, and those more prone to infection over time - understanding transfer dynamics will help us evaluate the entire spectrum of the disease, taking into account the effectiveness of risk groups and conditions that make the disease more severe and some public health interventions.
- Speeding up the evaluation of research therapeutics and vaccines using "Master Protocols". The rapid development of main protocols for clinical trials, will speed up by optimizing the potential of evaluating new research drugs, vaccines and diagnoses with evaluating what works and what does not work,

improving collaboration and comparison in different studies, facilitating ethical estimation.

- Maintaining a high degree of communication and interaction between funders for the implementation of critical research -the funders reaffirmed their current financial commitments to overcome this pandemic and decided that the priorities agreed in the Forum would help coordinate existing investments and mobilize additional resources in the coming days, weeks and months.
- Share virus materials, clinical samples and data broadly and quickly for emergency public health purposes - it was recognized that virus materials, clinical samples, and related data should be shared quickly for public health purposes immediately, and fair and fair access to any medicinal product or innovation developed using the materials should be part of such sharing (WHO, 2020c).

The main theme of the above suggestions is to share information about covid related effective diagnosis and treatments with all transparency among the countries of the world and innovative drug-diagnosis and to reach treatment-related kits, vaccine, medicines, etc. is based on the development of applications in a short time.

At the present time, there are no vaccines or therapeutics to treat/prevent COVID-19 disease. According to the 2019 Coronavirus Global Research And Innovation Forum; there is insufficient information about the clinic progression and severity of Covid-19

disease and the safety-efficacy of current candidate therapeutics for treatment. Therefore, there is an urgent need to prioritize candidate therapeutics in clinical trials to identify successful drugs/vaccaines candidates who can improve the clinical course of the disease and reduce mortality in affected areas (WHO, 2020c).

Between different therapeutic options in clinical practice, Remdesivir was considered as the primary treatment in the COVID-19 disease; in addition, antiretroviral drug (HIV protease inhibitors), ritonavir/lopinavir were investigated alone or in combination with Interferon combination (WHO, 2020c).

With this issue to the current priority therapeutics (Ritonavir/ Lopinavir, Remdesivir), other therapeutic candidates with potential for clinical evaluation need to be investigated (eg other re-use drugs, healing plasma, new compounds) (WHO, 2020c).

In the investigation of candidate therapeutics, great importance should be given to issues such as in vitro / in vivo activity against COVID-19, the route and duration of administration to the body, appropriate dosage and safety-efficacy ranges in humans. These data are revealed by clinical studies defined as clinical researches/trials[2].

[2]Trial: Trial could be descriptive as a small sample of the main research/ Main research could be divided into sub-group that named trial/Sub-research is being the part of main researches as trial.

1. CLINICAL RESEARCH

Clinical research; to reveal or confirm the clinical, pharmacological or other pharmacodynamic effects of one or more investigational products; identifying adverse events or reactions; to detect absorption, distribution, metabolism and excretion; studies conducted to investigate safety and effectiveness (TİTCK, 2013). These researches are designed to progressively assess whether a new drug or medicinal product candidate will be used in a larger population and these stages are named "Phase".

Each phase is designed to search for answers to specific questions for the investigational product. Each phase has a different purpose in the development of pharmaceuticals products and medicinal products and is structured according to the results of the previous phase. Phases have a process that starts with preclinical research and ends with post-clinical research. These studies are carried out within the framework of pre-determined and structured processes and this period covers an average of 10 years. These investigations are carried out in three main stages. These stages are (Ekinci, 2019);

a) Pre-clinical Researches
b) Clinical Researches
c) Post-clinical Researches

While developing a product/molecule, it passes through these stages respectively.

A. Pre-clinical Researches (Phase 0 Researches)

Pre-clinical researches are the studies that carried out in a laboratory environment. A new molecule, a compound can be considered as search efforts. Following this phase, pre-clinical tests and invitro experiments are carried out. This stage of clinical research could be identified as Phase-0 clinical trials (Ekinci, 2019). These clinical researches are the studies that carried out in laboratory environment and on experimental animals. Laboratory studies are included preclinical tests and in-vitro experiments that the emergence of a new compound (synthesis-screening).

B. Clinical Researches

Clinical research (this phase) is carried out in four stages. These stages are;

- Phase I Clinical Researches
- Phase II Clinical Researches
- Phase III Clinical Researches
- Phase IV Clinical Researches

While Phase I Clinical Researches, Phase II Clinical Researches and Phase III Clinical Researches are done before the investigational product is licensed; Phase-IV Clinical Researches are carried out after the investigational product is licensed. In the design of the phases; the amount of the investigational product, the number of individuals, the duration of the researches; differs in terms of to be tested the investigational product (See Table:2).

C. Post-Clinical Researches (Scientific-Observational Researches)

Epidemiological researches are the study of the distribution and determinants of health-related events and conditions of a particular community and the use of research results to control health problems (Hayran, 2016).

Epidemiological researches are done at roughly three levels; firstly, observational descriptive research to identify health-related events and situations; secondly, analytical research based on observations, to clarify cause-effect relationships and thirdly, to finalize cause-effect relationships and develop control methods are experimental/ intervention researches conducted (Hayran, 2016).

Epidemiological researches are the studies in which data on prescribed drugs and products are collected for larger populations and could be identified the latest phase of Phase Clinical IV researches.

Table 2: Research Types in Health

Clinical Study Phase	Aim	Species Type Tested	Operation time
PRE - CLINICAL RESEARCHES			
Laboratory Experiments		Molecular Compounds	Shows Variability
Phase-0	**Animal Experiments**	Animal Species	Shows Variability
CLINICAL RESEARCHES			
Phase--I	Determination of the appropriate dose range for safety and toxicity in healthy or sick volunteers *Phase Ia;* short-term study to understand the reliability of the research product *Phase Ib;* subsequent long-term and comprehensive research from Phase Ia	Generally healthy volunteers between 20 and 80	12 - 18 months
Phase--2	Phase IIa, determination of appropriate dose range for patient volunteers in terms of efficacy and safety To reveal the feasibility of Phase 3 studies in Phase IIb, controlled, randomized and double-blind studies	Volunteers from 100 to 300 patients	1 - 3 years
Phase--3	*Phase IIIa*, determining the safety-related parameters of the drug in the period until the new drug application is made to the official institution of the investigational product (side effect, etc.). Comparison with other drugs in terms of effectiveness-safety Phase IIIb determines the safety related parameters (side effect, therapeutic efficacy, etc.) between the new drug application and the approval period. Comparison with other drugs in terms of effectiveness-safety	A few hundred to several thousand sick volunteers	2 - 5 years
Phase--4	Post-marketing follow-up studies of the product that is licensed for the drug and the product considered as the drug	Large patient populations using the drug	Shows Variability
POST - CLINICAL RESEARCHES			
Epidemiological Research-Scientific-Observational Research		Large patient populations using the drug	Shows Variability

According to "Global research and innovation forum: towards a research roadmap"; the research priorities for clinical research for this outbreak and beyond are identified as follows:

Table 3: The Research Priorities For Clinical Research

Research priority	**Why?**	**What type of studies/research are needed?**
Develop in vitro and in vivo testing	Identify candidate therapeutics to be tested in clinical trials.	•Make repository list of laboratories holding isolated COVID-19. •Standardizing virus propagation protocols. • Develop adequate animal models from mice to NHPs. •Foster standardization and harmonization of in vitro/in vivo testing (e.g. cell lines, positive/negative controls). •Perform screening of repurposed products and discovery libraries. •Select existing and/or develop new monoclonal and polyclonal antibodies. Carry out preclinical evaluation, including for immunopathology. • Put data collected into repository to inform and adjust methods for preclinical and clinical testing.
Evaluate efficacy and safety in prophylactic use	Protect those at risk (e.g. health care workers) with antiviral agents. Reduce nosocomial transmission and to promote their licensing to facilitate access.	• Prophylaxis clinical trials (e.g. health care workers) according to Master Protocol.
Promote adequate supply of therapeutics showing efficacy	Facilitate fair, affordable and equitable access to treatment.	• Evaluate production capacity. • Foster technology transfer. • Confirm affordable and equitable access to all affected countries.
Evaluate safety and efficacy of candidate therapeutics throug randomized clinical trials	To identify therapeutics that can reduce mortality and improve clinical disease outcome and to promote their licensing to facilitate access.	• RCTs through Master protocols (according to the severity of the disease).
Investigate combination therapies	To maximize the efficacy ofthe treatment and reduce the risk of development of resistance.	• In vitro/in vivo studies for synergic effect of drugs combinations. • RCTs for combination therapies.

Source:http://origin.who.int.

There are major knowledge gaps around the disease of COVID-19 and its treatment options with therapeutic options. This study can support to "Midterm and Long Term Priorities for Controlling the Outbreak" by improving clinical results to maximize the availability of data

throughout a series of studies that pointed by WHO (WHO, 2020c). In this study, it was aimed to determine the current status and detailed information of the COVID clinical researches/trials in world and Turkey. Clinical trials data were taken from clinicaltrials.gov.tr[3]. With the heading “COVID”, clinicaltrials.gov.tr was searched and the data in this field were analyzed. This study is a descriptive and cross-sectional study. The data were made on the current data in the www.clinicaltrial.gov.tr. and recorded on 22.06.2020 were analyzed.

Clinical researches in the study was carried out according to two main titles Word and Turkey. Clinical researches, which are handled under two main titles, were also examined in detail to their “phases, gender and age groups”.

Total clinical trials give the number of clinical trials conducted in[4] worldwide. In this study, the number of clinical trial[5] consists of information about different (Recruiting, Enrolling by invitation, Active, not recruiting, Suspended, Terminated, Completed, Withdrawn, Unknown status etc.) processes of a trial.

[3] “Clinicaltrials.gov.tr” is a record of clinical trials. It is operated by the National Library of Medicine, the National Institute of Health of the United States, and is the largest clinical research database from 209 countries.

[4] In this study, the number of clinical trial consists of information about different (Recruiting, Enrolling by invitation, Active, not recruiting, Suspended, Terminated, Completed, Withdrawn, Unknown status etc.) processes of a trial. Therefore, the verb "conducted" was used in the evaluation of the studies' curent situation.

[5] COVID Clinical Trials In World consist : Not yet recruiting (727), Recruiting (1139), Enrolling by invitation (16), Active, not recruiting (112), Suspended (13), Terminated (5), Completed (148) Withdrawn (16) Unknown status (0) COVID Clinical Trials In Turkey consist Not yet recruiting (8), Recruiting (25), Enrolling by invitation (3), Active, not recruiting (6), Suspended (0), Terminated (0), Completed (17), Withdrawn (0), Unknown status(0).

The total number of clinical trials and the number of clinical trials to age, gender, and phases are differ. This situation is thought to result from the same clinical research being applied differently according to gender and age.

In the following sections of the study, the current status of COVID related clinical trials, distribution by phases, gender and age were detailed.

2. COVID RELATED CLINICAL TRIALS

343,237 clinical trials were conducted in the World. 81% of these clinical trials made in Americas (50%) and European countries (31%). 5% of clinical trials were made by Middle East, (%7) Asia countries, (%2) Pasificia.

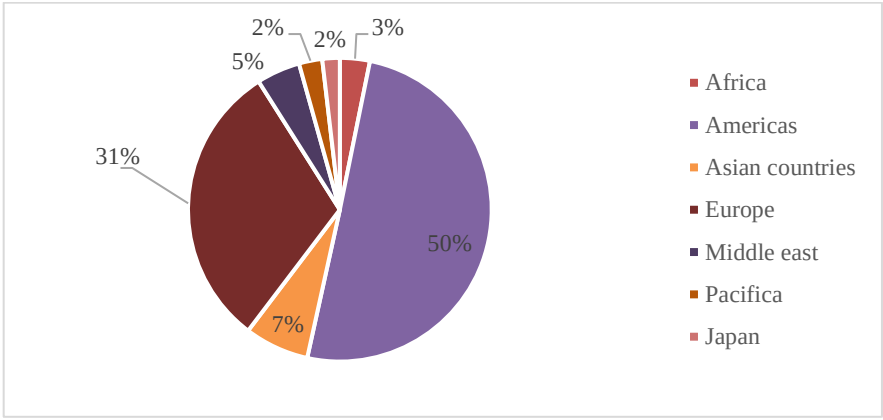

Chart 3: Total Clinical Trials by Region, World, 2020

In 2020, a total of 5,228 clinical trials were conducted in Turkey and the share of Turkey's total clinical trials in the world was 1.5%. Turkey

growth rate of the number of clinical trials is 95% in the last three years (Ekinci&Bakır, 2017).

Table 4: COVID Clinical Trials, 2020

	Total Clinical Trials	Covid Clinical Trials
World	343,237	2,240
Turkey	5,228	59

2,240 Covid Clinical Trial has been conducted in the World and this rate was corresponded to 0,65% of the total clinical research conducted in the world. In addition, 78% of these studies were conducted in Europe (45%), America (33%) and Asia (11%).

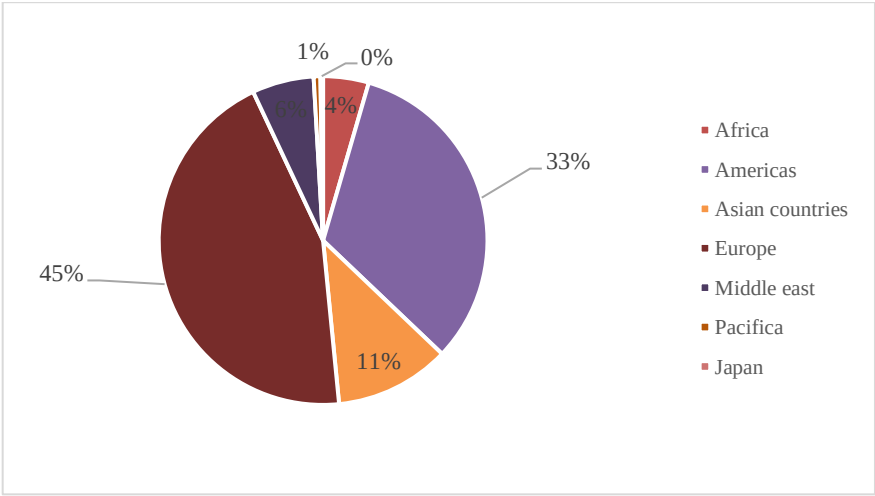

Chart 4: COVID Clinical Trials according to Region, World 2020

Total of 59 Covid Clinical Trial has being conducted in Turkey and its share of in the Worlds' Covid Clinical Trial was 2,6 %. And also the

share of Turkeys' Covid Clinical Trial in a total clinical trials conducted in Turkey is 1.1%.

3. ACCORDING TO PHASES

The distribution of world Covid Clinical Trial according to its phases[6] was evaluated in that respectively; Early Phase 1 (2%), Phase 1 (9%), Phase 2 (35%), Phase 3 (21%), Phase 4 (5%), Not applicable status (28%).

Table 5: COVID Clinical Trials according to Phase, 2020

	World (n)	**Turkey (n)**
Early Phase 1	22	0
Phase 1	125	6
Phase 2	498	2
Phase 3	306	1
Phase 4	68	1
Not Applicable	402	10

Early phase studies were constituted a very low rate, like 2% of total trials (see Chart 5). In phases, “Not Applicable” status share was 28% in total Covid Clinical Trial.

[6] In phases, without phase 1-2-3-4, there is a section named “Not Applicable” status in clinicaltrials.gov.tr. Not Applicable means that describes trials without FDA-defined phases, including trials of devices or behavioral interventions.

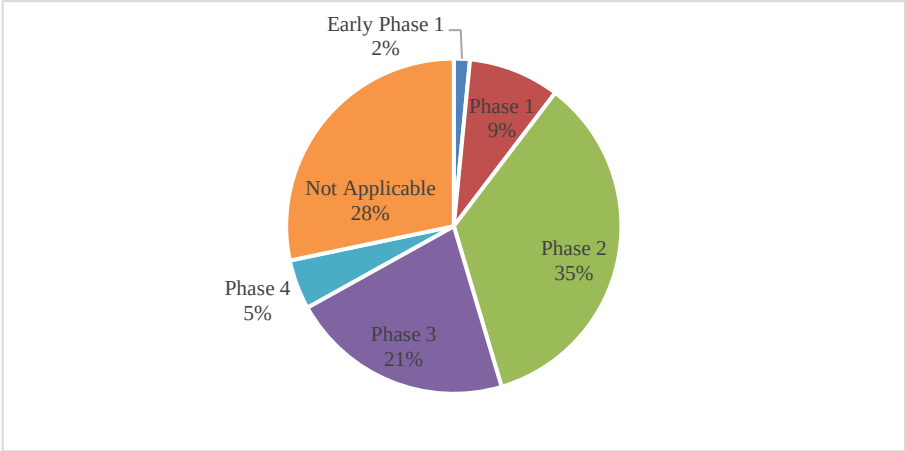

Chart 5: COVID Clinical Trials according to Phase World, 2020

The distribution of Turkey Covid Clinical Trial according to its phases[7] was evaluated in that respectively; Early Phase 1 (0%), Phase 1 (30%), Phase 2 (10%), Phase 3 (5%), Phase 4 (5%) and the not applicable status (50%).

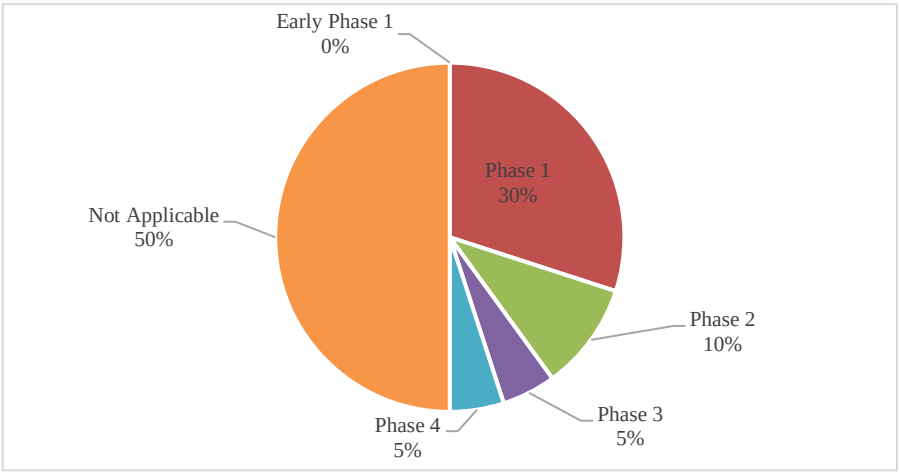

Chart 6: COVID Clinical Trials according to Phase Turkey, 2020

[7] Clinical research evaluation according to the phases in Turkey; It was done through 20 covid clinical studies that located in the clinical.gov.tr.

4. ACCORDING TO GENDER

The distribution according to gender of Covid Clinical Trial in the world and Turkey were close to each other as numerical value between men and women.

Table 6: Covid Clinical Trials according to Gender, 2020

	World	Turkey
Female	2230	55
Male	2186	47

In the evaluation of the distribution of Covid clinical trials according to gender was given Table 7. According to table;

Table 7: COVID Clinical Trials According To Gender, 2020

	World Female	Turkey Female	World Male	Turkey Male
Early Phase 1	22	0	22	0
Phase 1	120	2	125	6
Phase 2	497	2	497	2
Phase 3	306	1	304	1
Phase 4	68	1	68	1
Not Applicable	401	10	390	10

In female group 35% Phase 2 trials are conducted in the world and followed by Not applicable (28%) and phase 3 trials (22%). In the total clinical trials in female the rate of Early Phase 1 and Phase 1 trials share in 10% and Phase 4 trials share 5%.

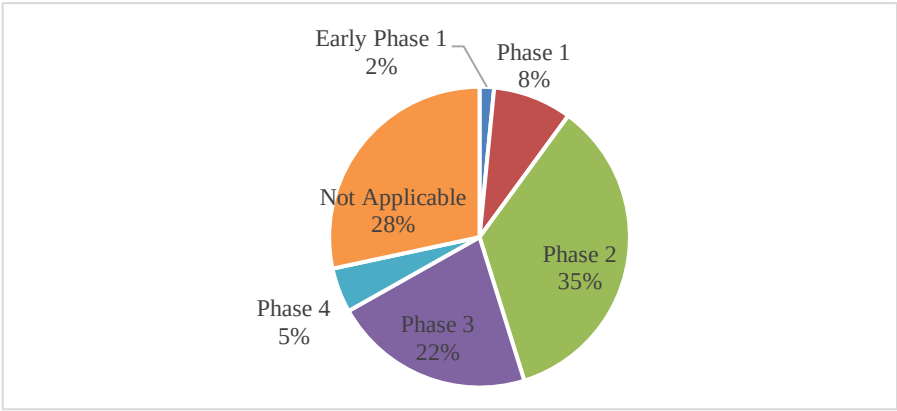

Chart 7: Covid Clinical Trials According To Female In Word, 2020

In male group 35% Phase 2 trials are conducted in the world and followed by phase 3 trials (22%) and Not applicable (28%). In the total clinical trials in female, the rate of Early Phase 1 and Phase 1 trials share in 10% and Phase 4 trials share 5%.

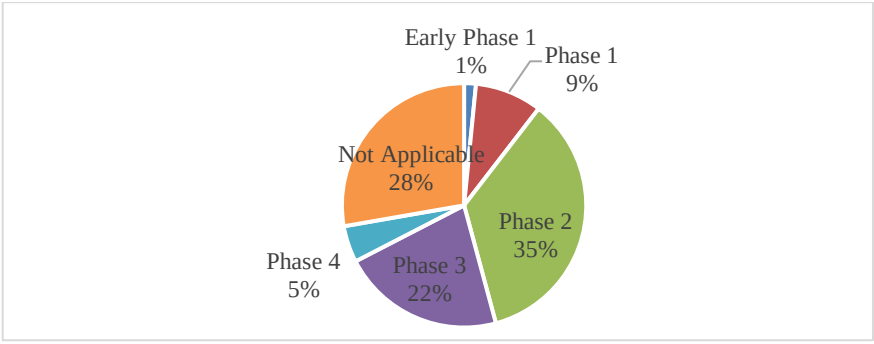

Chart 8: Covid Clinical Trials according to Male In Word, 2020

In female group[8] 13% Phase 2 trials are conducted in Turkey and followed by phase 3 trials (6%), phase 4 trials (6%) and Not applicable (63%). In the total clinical trials in female the rate of Phase

[8] Clinical research evaluation according to gender –female group- in Turkey; it was done through 16 covid clinical studies that located in the clinical.gov.tr.

1 trials share in 12% and beside this result it was evaluated that there was no Early Phase 1 trials studied in Turkey.

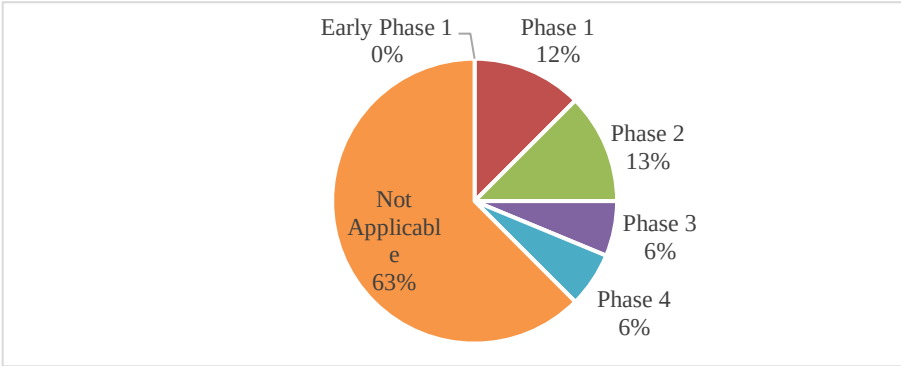

Chart 9: Covid Clinical Trials according to Female In Turkey, 2020

In male group[9] (30%) Phase 1 trials are conducted in Turkey and followed by phase 2 trials (10%), phase 3 trials (5%), phase 4 trials (5%) and Not applicable (50%). In the total clinical trials in Male the rate of Phase 1 trials share in 30% and beside this result it was evaluated that there was no Early Phase 1 trials studied in Turkey.

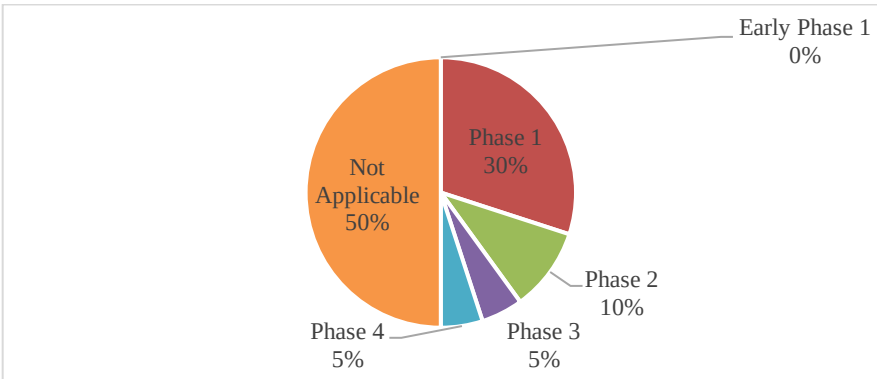

Chart 10: Covid Clinical Trials according to Male In Turkey, 2020

[9] Clinical research evaluation according to gender –male group- in Turkey; it was done through 20 covid clinical studies that located in the clinical.gov.tr.

5. ACCORDING TO AGE-PHASES

In this section, Covid clinical trials current status were evaluated according to age in the world and Turkey and also calculated values are given in this section.

Table 8: Distribution of Covid Clinical Trials according to Age, 2020

Age	Covid Clinical Trials World	Covid Clinical Trials Turkey
Birth-17	135	0
18-65	1397	19
66 and upper	1340	12

48% of the clinical trials were conducted in the world was in the age range of 18-65, 47% in the age range of 66 and upper age, 5% in the age range of birth-17 (see Chart 11).

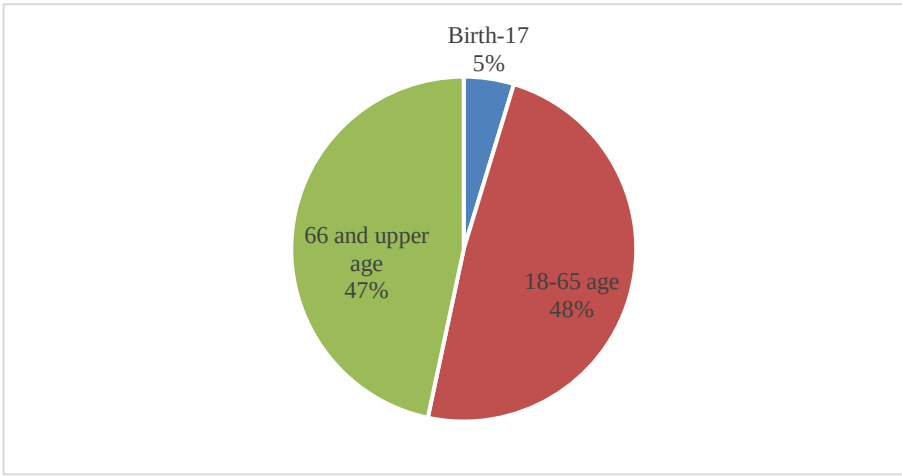

Chart 11: Covid Clinical Trials according to Age, World, 2020

61% of the clinical trials were conducted in the Turkey was in the age range of 18-65, 39% in the age range of 66 and upper age beside this result there was no Covid clinical trials conducted in the age range of birth-17 (see Chart 12).

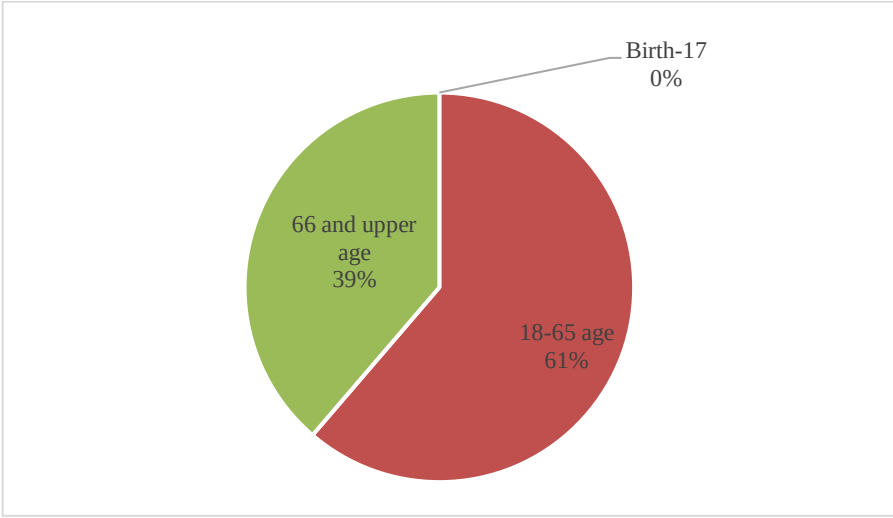

Chart 12: Covid Clinical Trials according to Age, Turkey, 2020

In the evaluation of the distribution of Covid clinical trials according to phases and age groups were given Table 9.

Table 9: COVID Clinical Trials according to Age and Phase, 2020

Phase	Age	World	Turkey
Early Phase 1	Birth-17	0	0
	18-65	21	0
	66 and upper	22	0
Phase 1	Birth-17	10	0
	18-65	125	6
	66 and upper	104	1
Phase 2	Birth-17	36	0
	18-65	493	2
	66 and upper	478	1
Phase 3	Birth-17	39	0
	18-65	299	1
	66 and upper	296	1
Phase 4	Birth-17	2	0
	18-65	68	1
	66 and upper	66	1
Not Applicable	Birth-17	48	0
	18-65	391	9
	66 and upper	374	8

In the World;

- In the age range of birth and 17; Phase 3 (29%) and Phase 2 (27%) clinical trials were the most frequently studied phase.
- in the age range of 18-65; Phase 2 (35%) and Phase 3 (21%) clinical trials were the most frequently studied phase.
- in the age range of 66 and upper; Phase 2 (36%) and Phase 3 (22%) clinical trials were the most frequently studied phase.

In Turkey;

- clinical research information in the 0-17 age group was not available
- in the age range of 18-65; Phase 1 (32%) was the most frequently studied phase
- in the age range of 66 and upper; distribution of clinical trials by all phases is equal to each other (about 8%)

6. CONCLUSIONS

The results obtained from this study for Covid related clinical trials are as follows:

While the countries of America are in the first place in the distribution of Covid-19 cases by region, European countries are in the second place and the same is valid for covid deaths. Covid-related cases and deaths were less seen in Eastern Mediterranean, South-East Asia, Africa and Western Pacific compared to these two regions. One of this reason could be related with population density.

The highest share in total clinical trials in the world was Americas, than European countries were in the second place. Turkey's share in the world received from total clinical trials was found to be 1.5% and Turkey growth rate of the number of total clinical trials was 95% in the last three years (Ekinci&Bakır, 2017). The highest share in Covid clinical trials in the world was conducted in European countries (45%), than Americas (33%) were in the second place.

The ratio of Covid Clinical Trial in total clinical trials in the world was 0.65%. The ratio of Turkey's Covid Clinical Trial to the total Covid Clinical Trial trials in the world was found 2.6% indicating. And also the ratio of Turkey's Covid Clinical Trials in the total Covid Clinical Trial clinical trials in Turkey was found 1.1%. However, since this ratio is 0.65% in the world; Turkey's Covid Clinical Trials' share in the world was can be evaluated high.

- Covid Clinical Trial in the world, Phase 2 clinical trials (35%) and Phase 3 clinical trials (21%) has been foregrounded.
- In Turkey Phase 1 Covid Clinical Trial was conducted mostly (30%). It can be interpreted that Turkey has started later Covid Clinical Trial according to world scale
- The distribution according to gender of Covid Clinical Trial in the world and Turkey were close to each other as numerical value between men and women.
- Distribution of phases to gender; Covid Clinical Trial in the world was dispersed similarly between men and women.
- Distribution of Covid Clinical Trial phases, Turkey has differences between in men and women groups. In Turkey expecially in female group Phase 2 trials (13%) in male group Phase 1 trials (30%) were conducted.
- In the World; 95% of total clinical trials in the world were carried out with adults and also distribution of phases according to 18-65 and 66-upper age; Covid Clinical Trial phases in the world was dispersed similarly.
- In Turkey clinical researches were not carried out under 18 age; in the age range of 18-65; Phase 1 (32%) was the most frequently studied phase.
- Covid Clinical Trial are mainly made in European countries. Phase 2-3 stands out in Covid Clinical Trial in the World. Considering the period of completing of phases, it can be foreseen to access the innovative Covid-19 related treatments

requires a little more time. The number of completed clinical trials were 170 in World and 17 in Turkey till now.

- It also shows that the status of phase 1-2 trials are acting outside the general accepted timing of the phases. It can be evaluated that in Covid-19 related the phases are completing in a short time.
- In the evaluation according to gender, we can conclude that phase studies in the Covid-19 field are performed similarly among men and women, therefore, gender is not an important factor in the phase studies conducted.

An evaluation for Covıd Clinical Trials in Turkey;

As of June 22, 2020;.while the number of 187,685 confirmed covid related cases; the number of 4,950 patients died due to the Covid - 19. Number of 59 Covid related clinical trials have been identified in Turkey[10]. In the distribution of these studies by provinces, Istanbul ranked first with 43 studies. Then the number of covid related cinical trials were determined Ankara, Konya, Bursa, Gaziantep, Erzincan, İzmir, Kayseri, Rize and Uşak respectively (4, 3, 2, 2, 1, 1, 1, 1, 1). Covid Clinical Trials in Turkey consist "Not yet recruiting (8), Recruiting (25), Enrolling by invitation (3), Active, not recruiting (6), Completed (17)".

The current situation in Turkey; clinical trials are carried out with individual efforts of university hospitals and the private sector[11].

[10] See Annex 2 to detailed information about the COVID-19 clinical trials in Turkey
[11] In total, good clinical research practice center exist in Turkey is 5 as follows;

Clinical trials in hospitals affiliated to the Ministry of Health are carried out with individual efforts in cooperation with the university. 65 of 879 hospitals affiliated to Ministry of Health in Turkey serve as training and research hospitals under the name of A1 hospitals. But there is no professional approach or institutionalization for the management of clinical trials in these hospitals (except Istanbul Mehmet Akif Ersoy Thoracic and Vascular Surgery Training and Research Hospital) nd this can be recieved that Turkey has cretaed a low performans in the clinical trials generally. Clinical trials are seriously audited studies and must meet certain standards in the areas of application. In the clinical trials conducted with the support of the public and private industry in the world but there is insufficient infrastructure in Turkey[12].

Countries have to do everything to stop Covid-19 related cases from becoming becoming explosive outbreaks. The countries have to engage everyone in the respons to put the capacities for testing and diagnosis, isolation, contact tracing and quarantine.

• Kocaeli University Medical Faculty Clinical Research Unit • Ankara University Medical Faculty Hematology Discipline Clinical Research Unit • Ege University PROKOM • Istanbul University Clinical Research and Excellence Center • Istanbul Mehmet Akif Ersoy Thoracic, Cardiac and Vascular Training and Research Hospital Clinical Research Center (include Phase I Clinical Research Center)

[12]For improving and development health research and development field in Turkey the related plans/programs are as follows:

• Ministry of Health 2010-2014 Strategic Plan • National Science, Technology and Innovation Strategy (NSTIS) 2011-2016 • 10th Development Plan Structural Transformation Program Action Plan in Healthcare Industries • National Science and Technology Policies 2003-2023 Strategy Document • Turkey Pharmaceutical Sector Strategy and Action Plan • Ministry of Health Strategic Action Plan 2014-2017 • Presidential 100 Day Program, Ankara

This study can facilitate expedited discovery and early development efforts in Covid Clinical Trials while also creating a foundation for longer-term research and development beyond the current outbreak.

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Annex 1. Countries, territories or areas with reported laboratory-confirmed COVID-19 cases and deaths, by WHO region. Data as of 10 AM CEST, 22 June 2020*

	Total confirmed cases	**Total Deaths**		**Total confirmed cases**	**Total Deaths**
Africa			**Europe**		
South Africa	97,302	1,93	Russian Federation	592,28	8,206
Nigeria	20,244	518	The United Kingdom	304,335	42,632
Ghana	14,154	85	Spain	246,272	28,323
Algeria	11,771	845	Italy	238,499	34,634
Cameroon	11,281	300	Germany	190,359	8,895
Cote d'Ivoire	7,492	54	Turkey	187,685	4,950
Senegal	5,888	84	France	154,567	29,571
Democratic Republic of the Congo	5,825	129	Belgium	60,55	9,696
Guinea	4,998	27	Belarus	58,505	346
Kenya	4,738	123	Sweden	56,043	5,053
Ethiopia	4,532	74	Netherlands	49,593	6,09
Gabon	4,428	34	Portugal	39,133	1,53
Mauritania	2,813	108	Ukraine	37,241	1,012

Central African Republic	2,808	23	Poland	31,931	1,356
Mali	1,961	111	Switzerland	31,217	1,68
South Sudan	1,882	34	Ireland	25,379	1,715
Madagascar	1,596	14	Romania	24,045	1,512
Guinea-Bissau	1,512	16	Israel	20,652	306
Zambia	1,43	11	Armenia	20,588	360
Sierra Leone	1,327	55	Kazakhstan	17,732	120
Equatorial Guinea	1,043	12	Austria	17,285	690
Niger	1,036	67	Republic of Moldova	14,2	475
Burkina Faso	901	53	Serbia	12,894	261
Cabo Verde	890	8	Azerbaijan	12,729	154
Congo	883	27	Denmark	12,391	600
Chad	858	74	Czechia	10,498	336
Benin	765	12	Norway	8,708	244
Uganda	755	0	Finland	7,143	326
Mozambique	733	5	Uzbekistan	6,358	19
Malawi	730	11	Tajikistan	5,457	52
Rwanda	728	2	North Macedonia	5,106	238
Eswatini	635	5	Luxembourg	4,12	110
Liberia	626	34	Hungary	4,102	572
Togo	569	13	Bulgaria	3,905	199
United Republic of Tanzania	509	21	Bosnia and Herzegovina	3,431	169
Zimbabwe	489	6	Kyrgyzstan	3,356	40
Sao Tome and Principe	388	10	Greece	3,266	190
Mauritius	337	10	Croatia	2,317	107
Comoros	247	5	Albania	1,995	44
Angola	176	9	Estonia	1,981	69
Burundi	144	1	Iceland	1,823	10
Eritrea	143	0	Lithuania	1,798	76
Botswana	89	1	Slovakia	1,587	28
Namibia	55	0	Slovenia	1,52	109
Gambia	37	2	Latvia	1,111	30
Seychelles	11	0	Cyprus	986	19
Lesotho	4	0	Georgia	908	14
Mayotte Territories	2,404	31	Andorra	805	52
Réunion Territories	506	1	San Marino	713	42
Americas			Malta	665	9
United States of America	2,241,178	119,453	Montenegro	362	9
Brazil	1,067,579	49,976	Monaco	99	1
Peru	251,338	7,861	Liechtenstein	83	1
Chile	242,355	4,479	Holy See	12	0
Mexico	175,202	20,781	Territoriesii Kosovo[1]	2,126	26

Canada	101,019	8,41	Isle of Man Territories	336	24
Colombia	65,633	2,126	Jersey Territories	318	31
Ecuador	50,64	4,223	Guernsey Territories	252	13
Argentina	41,204	992	Faroe Islands Territories	187	0
Dominican Republic	26,677	662	Gibraltar Territories	176	0
Panama	25,222	493	Greenland Territories	13	0
Bolivia (Plurinational State of)	23,512	740	**Western Pacific**		
Guatemala	12,755	514	China	85,018	4,646
Honduras	12,306	358	Singapore	42,095	26
Haiti	5,077	88	Philippines	30,052	1,169
El Salvador	4,626	98	Japan	17,916	953
Venezuela (Bolivarian Republic of)	3,79	33	Republic of Korea	12,438	280
Cuba	2,312	85	Malaysia	8,572	121
Costa Rica	2,127	12	Australia	7,461	102
Nicaragua	2,014	64	New Zealand	1,163	22
Paraguay	1,379	13	Viet Nam	349	0
Uruguay	859	25	Mongolia	206	0
Jamaica	657	10	Brunei Darussalam	141	3
Suriname	302	8	Cambodia	129	0
Guyana	183	12	Lao People's Democratic Republic	19	0
Trinidad and Tobago	123	8	Fiji	18	0
Bahamas	104	11	Papua New Guinea	9	0
Barbados	97	7	Guam Territoriesii	214	5
Saint Vincent and the Grenadines	29	0	French Polynesia Territoriesii	60	0
Antigua and Barbuda	26	3	Northern Mariana Islands Territoriesii (Commonwealth of the	30	2
Grenada	23	0	New Caledonia Territoriesii	21	0
Belize	22	2	**South-East Asia**		
Saint Lucia	19	0	India	425,282	13,699
Dominica	18	0	Bangladesh	112,306	1,464
Saint Kitts and Nevis	15	0	Indonesia	45,891	2,465
Puerto Rico	6,525	149	Nepal	9,026	23
French Guian	2,441	6	Thailand	3,151	58
Martinique	236	14	Maldives	2,203	8

Cayman Islands	195	1	Sri Lanka	1,95	11
Guadeloupe	174	14	Myanmar	290	6
Bermuda	146	9	Bhutan	68	0
Aruba	101	3	Timor-Leste	24	0
Sint Maarten	77	15	**Subtotal for all regions**	**8,859,590**	**465,727**
United States Virgin Islands	76	6	**Other***	**741**	**13**
Saint Martin	42	3	**Grand total**	**8,860,331**	**465,740**
Curaçao	23	1			
Falkland Islands (Malvinas)	13	0			
Turks and Caicos Islands	12	1			
Montserrat	11	1			
British Virgin Islands	8	1			
Bonaire, Sint Eustatius and Saba	7	0			
Saint Barthelemy	6	0			
Anguilla	3	0			
Saint Pierre and Miquelon	1	0			
Eastern Mediterranean					
Iran (Islamic Republic of)	204,952	9,623			
Pakistan	181,088	3,59			
Saudi Arabia	157,612	1,267			
Qatar	87,369	98			
Egypt	55,233	2,193			
United Arab Emirates	44,925	302			
Kuwait	39,65	326			
Iraq	30,868	1,1			
Oman	29,471	131			
Afghanistan	29,143	598			
Bahrain	21,764	63			
Morocco	9,977	214			
Sudan	8,58	521			
Djibouti	4,582	45			
Somalia	2,779	90			
Lebanon	1,587	32			
Tunisia	1,157	50			
Jordan	1,033	9			
Yemen	945	257			
Libya	571	10			
Syrian Arab Republic	204	7			
Territoriesii					
occupied Palestinian territory	1,028	5			

Annex 2: Covıd Clinical Trials in Turkey, 06/22/2020

	Title	Status	Conditions	Interventions	Locations
1	Do Vitamin D Levels R eally Correlated With Di sease Severity in COVID-19 Patients?	Enrolling by invitation	COVID	•Dietary Supplement: vitamin d	•Bursa City Hospital, Bursa Dogankoy, Turkey
2	Dornase Alpha for the T reatment of COVID-19	Recruiting	COVID-19	•Drug: Pulmozyme	•Acıbadem Altunizade Hospital, Istanbul, Turkey
3	Evaluation of Vaginal Fl uid for Covid-19 Positivity in Women With Positive Nasofaren geal Covid-19 Test	Recruiting	•COVID •Sars-CoV2	•Diagnostic Test: Vaginal fluid Covid-19 PCR test	•Acibadem Maslak Hospital, Istanbul, Turkey
4	Impact of COVID19 Pa ndemic on Perceived Ex ercise Benefits and Barriers	Completed	•COVID •Isolation, Social	• Other: Online Survey	•Istanbul Okan University, Istanbul, Turkey
5	Evaluation of Clinical P arameters on Admission Medications in Covid-19 Pneumonia (Corona Virus Disease 2019)	Completed	•Covid-19	•Drug: ACE Inhibitors and Calcium Channel Blockers	• Vital Hospital, Bahcelievler, Istanbul, Turkey
6	COVID 19 Pandemic and Femal e Sexual Behavior	Completed	•Sexual Behaviour • COVID	•Behavioral: fsfi survey	•Haseki Training and Research Hospital, Istanbul, Turkey
7	The Utility of Bedside L ung Ultrasonography on Diagnosis of COVID-19	Recruiting	•COVID •Pneumonia Viral	•Device: Bedside lung ultrasound	•Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey
8	Treatment of Angiotensi n Peptide (1-7) for COVID-19	Recruiting	•COVID-19	•Biological: Biological/Va ccine: Angiotensin peptide (1-7) derived plasma	• Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey
9	Effect of Quercetin on P rophylaxis and Treatme nt of COVID-19	Recruiting	•COVID-19	•Dietary Supplement: Quercetin Prophylaxis •Dietary Supplement: Quercetin Treatment	• Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey
10	Pulmonary Rehabilitatio n in Post-Acute Period of COVID -19 Infection	Completed	•COVID-19	•Other: Rehabilitation	•Istanbul Bilgi University, Istanbul, Turkey

11	Thorax Computed Tomography Severity Score and Outcome in COVID-19 Patients	Recruiting	•COVID-19	•Diagnostic Test: CT-Scan	•Tepecik Training and Research Hospital, Izmir, Izmir, Konak, Turkey
12	Evaluation of Covid 19 Knowledge Anxiety and Expectation Levels of Turkish Physicians, Survey Study	Completed	•COVID-19 • Physician-Patient Relations	•Behavioral: turkish physicians	•Pinar Yalcin Bahat, stanbul, Istanbul, Turkey
13	D-Dimer Levels in Pregnant With COVID-19	Completed	•COVID-19 •D-dimer	• Other: Blood D-dimer assay	• Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turgut Ozal, Turkey
14	Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-19	Recruiting	•Sars-CoV2 • OVID-19	•Drug: Favipiravir (3200 mg + 1200 mg) •Drug: Favipiravir (3600mg+ 1600 mg) •Drug: Favipiravir (3200 mg + 1200 mg) combined with Hydroxychloroquine •Drug: Favipiravir (3200 mg + 1200 mg) combined with Azithromycin •Drug: Hydroxychloroquine •Drug: Hydroxychloroquine combined with Azithromycin	•Hacettepe University, School of Medicine, Ankara, Turkey
15	COVID-19 PCR Test Results in Asymptomatic Pregnants	Completed	•COVID-19 •Asymptomatic Pregnant	•Diagnostic Test: Reverse transcription polymerase chain reaction	•Istanbul Medipol University, Istanbul, Turkey
16	Evaluation of Covid 19 Anxiety in Endometriosis Patients	Completed	•Endometriosis • Covid19		• Pinar Yalcin Bahat, Istanbul, Istanbul, Turkey
17	The Effectiveness of Telerehabilitation-Based Physiotherapy in COVID 19 Patients	Recruiting	•Covid19 •Telerehabilitation •Physical Therapy	•Other: Physiotherapy	•University of Health Sciences Turkey, Istanbul, Turkey

18	Maternal And Neonatal Outcome of Pregnant Patients With COVID-19 in Istanbul, Turkey: A Single-Center, Retrospective, Descriptive Study	Completed	•Covid19 • Maternal-Fetal Relations	•Other: newborns from covid 19 positive mothers	• Pinar Yalcin Bahat, Istanbul, İstanbul, Turkey
19	"Investigation of the Relationship Between New Coronary Virus Disease (COVID19) and Anxiety and DepressiveSymptoms in Pregnant Women"	Active, not recruiting	•COVID •Anxiety •Depression ,Postpartum	•Behavioral: covid-19 positive pregnant women	• Pinar Yalcin Bahat, Istanbul, Istanbul, Turkey
20	Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid 19 Positive Pregnant Women	Active, not recruiting	•COVID •Zinc Deficieny •Vitamin D Deficiency	•Other: Serum zinc, vitamin d vitamin b12 levels .	• Pinar Yalcin Bahat, Istanbul, Istanbul, Turkey
21	Familial Mediterranean Fever and Behçet: Analysis Before and After Covid19 Pandemic	Enrolling by invitation	•Behcet Disease •COVID • FMF	•Other: it will be compared pain, sleep, fatigue, physical activity level and quality of life and questioning exercise habits before and after the covid-19 outbreak in patients with Behçet and FMF.	• Istanbul, Istanbul, Bakırköy, Turkey
22	Postpartum Sexual Function in Pregnant Women With COVID-19	Recruiting	•COVID-19 •Dyspareunia •Postpartum Period		•Kanuni Sultan Suleyman Training and Research Hospital, ıstanbul, Halkali, Turkey
23	Postoperative Recovery Index, Patient Expectations and Satisfaction With Prenatal Care Instrument in Pregnant patients With COVID-19	Recruiting	•COVID-19 •Prenatal Care •Postoperative Care		•Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Halkali, Turkey
24	Physical Activity Level, Stress Level, Sleep Quality in Pregnant Women During Covid-19 Quarantine	Not yet recruiting	•Covid-19 •Coronavirus Infection •Pregnancy Related	•Other: Survey	•Istanbul University - Cerrahpaşa, Istanbul, Turkey

25	Prognosis in Pregnant With COVID-19	Completed	•COVID-19 •Prognostic Factor •Pregnancy	•Diagnostic Test: imaging, blood tests	•Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Halkali, Turkey
26	Characteristics of Neonatal Covid-19 in Turkey	Recruiting	•COVID-19 •Neonatal Disease • Healthy		• Recep Tayyip Erdogan University Medical School, Rize, Turkey
27	Impact of COVID-19 Pandemic on Depression and Quality of Life	Completed	•Depression •Quality of Life •Covid 19 •Social Isolation	•Other: Online survey	• Okan University, Istanbul, Turkey
28	Menstrual Cycle Characteristics of Healthcare Professionals	Recruiting	•Menstrual Irregularity •Covid 19		•University of Health Sciences Turkey, Istanbul, Turkey
29	Physical Rehabilitation in ICU in ARDS Patients With COVID-19	Completed	•COVID-19 •Acute Respiratory Distress Syndrome •Rehabilitation •Intensive Care Unit Acquired Weakness •Critical Illnes Polyneuromyopathy		•Koc University School of Medicine, Istanbul, Turkey
30	Investigation of Fatigue, Physical Activity, Sleep Quality and Anxiety Levels	Completed	•Multiple Sclerosis •Covid-19		•Ankara Yıdırım Beyazıt University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Ankara, Turkey
31	Obstructive Sleep Apnea & Covid-19 Outcomes	Recruiting	•COVID •Obstructive Sleep Apne •Pneumonia	•Diagnostic Test: Polysomnography	•Koc University, Istanbul, Turkey •Koc Healthcare Istanbul American Hospital, #stanbul, Turkey •Marmara University Pendik Education and Research Hospital, Istanbul, Turkey

32	Clinical Use of Stem Cells for the Treatment of Covid-19	Recruiting	•Covid19 •Pneumonia •Multiple Organ Failur •Corona Virus Infection	•Biological: MSC Treatment •Biological: Saline Control	• Istinye University, Istanbul, Turkey •SBÜ Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Istanbul, Turkey
33	Change in the Ratio of Mean Platelet Volume (MPV) to Platellet(PLT) in Covid-19 Pneumonia Patients	Recruiting	•Coronavirus Infection	•Other: observation of covid 19 pneumonia	•Gaziosmanpaşa TREH, Istanbul, Gaziosmanpaşa, Turkey
34	Extracellular Water in Covid 19 Pneumonia	Recruiting	•Extracellular Fluid Alteration •Corona Virus Infection	•Device: N#CaS	•Gaziosmanpaşa TREH, Istanbul, Gaziosmanpaşa, Turkey
35	Epigenetic Tool as Prognostic Predictors in Covid19	Recruiting	•Prognosis	•Other: Taking biological samples	• Bakirkoy Dr. Sadi Konuk Research and Training hospital, Istanbul, Turkey
36	Thrombosis Risk Assessment and Clinical Presentation of Covid-19 Pneumonia	Not yet recruiting	•Corona Virus Infecton •Thromboembolic Disease		•Vital Hospital, Bahcelievler, Istanbul, Turkey
37	Telerehabilitation in Individuals Over 65 Years of Age Having Social Isolation Due to Coronavirus (Covid-19)	Not yet recruiting	•Telerehabilitation	•Other: Telerehabilitation	•Istanbul university Cerrahpasa, Istanbul, Turkey
38	The Use of Lung Ultrasonography in COVID-19 Patients	Recruiting	•Ultrasonography	•Behavioral: mechanial ventilator settings and position	•Gazoosmanpasa Education and Research Hospital, Istanbul, Turkey
39	COVID-19 Specific T Cell Derived Exosomes (CSTC-Exo)	Active, not recruiting	•Corona Virus Infection •Pneumonia	•Biological: COVID-19 Specific T Cell derived exosoms (CSTC-Exo)	•GENKOK, Kayseri, Melikgazi, Turkey
40	Spironolactone in Covid -19 Induced ARDS	Not yet recruiting	•Respiratory Distress Syndrome, Adult	•Drug: Spironolactone 100mg •Drug: Placebo oral tablet	•Istanbul University-Cerrahpaşa, Istanbul, Turkey

41	Ozone Therapy in the Prevention of COVID-19 Infection	Completed	•Corona Virus Infection		•Kardelen Gencer Atalay, Istanbul, Turkey
42	" The Abdominal Crunch Position for COVID-19 Patients "	Completed	•Anesthesia, Spinal	•Other: Spinal Anesthesia Position	• Yasin Tire, Konya, Meram, Turkey
43	Clinical Characteristics of Critically Ill Patients With COVID-19	Recruiting	•Coronavirus Infection •Critical Illnes •Characteristics Disese	•Other: File Scanning	• Konya Trainig and Research Hospital, Konya, Turkey
44	Evaluation of the Fluid Response of SARS-CoV-2 (COVID-19) Patients in Intensive Care; Pleth Variability Index	Not yet recruiting	•Pleth Vaiability Index	•Diagnostic Test: Pleth variability index	•Erzincan University, Erzincan, Turkey
45	Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Recruiting	•Pneumonitis •Coronavirus Infection	•Drug: Plaquenl 200Mg Tablet	• Istinye University Medical School, Istanbul, Turkey
46	Social Media and Covid 19 Pandemic	Enrolling by invitation	•Social Media •Corona Virus Infection	•Behavioral: survey	•Bahar Yuksel, Istanbul, Turkey •Haseki Training and Research Hospital, Istanbul, Turkey
47	HFNC Treatment in COVID-19 Pneumonia	Recruiting	•Coronavirus Infection •Pneumonia,Viral •Acute Respratory Failue	• Device: high flow nasal cannula device	• Sisli Etfal Research and Training Hospital, Istanbul, Turkey •Sisli Etfal Research and Training Hospital, Istanbul, Turkey
48	The Development of Pancreatic Injury in the Course of Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Completed	•Panceatitis	•Other: biochemcal analysis	• Usak University Training and Research Hospital, Usak, Turkey
49	Haemoglobin Concentration on COVID-19	Recruiting	•Corona Virus Infecton	• Other: File scanning	• Konya Training and Research Hospital, Konya, Turkey
50	CoV-ICU Score, Intensive Care Unit, SARS-CoV-2	Recruiting	•Coronavirus as the Caus of Diseses Classified Elsewhere	•Other: COVIU	• Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Yildirim, Turkey

51	Comparison of New Coronavirus (COVID-19) Awareness in Individuals of Different Age Groups: Analysis of Turkey	Not yet recruiting	• Healthy		•Istanbul University-Cerrahpasa, Istanbul, Turkey
52	Effects of Social Isolation From Coronavirus; on Physical Activity, Quality of Life and Stress	Not yet recruiting	•Healthy People	•Other: Determnation of physical activity, quality of life, stress levels of isolated people at home with the danger of corona irus.	• Istanbul University Cerrahpasa, Istanbul, Turkey
53	Video-Based Exercises and Well-Being During Social Isolation	Completed	•Social Isolation •Physical Inactivit •Well-Being	• Other: Video based aerobic exercise	•Biruni University, Istanbul,Turkey •Istanbul University Cerrahpasa,Istanbul, Turkey
54	Emotional Freedom Technique (EFT) Effect on Nurses	Recruiting	•Stress •Anxiety •Burnout, Caregiver	•Behavioral: Emotioal Freedm Techniue	•Medeniyet University, Istanbul, Turkey
55	The Covid-19 HEalth caRe wOrkErS (HEROES) Study	Recruiting	•Covid-19 •Mental Health Disorder •Stress Disorder •Anxiety •Depression •SARS-CoV-2	•Other: Exposue to the SARS-CoV-2 and its consequences	•Columbia University, New York, New York, United States •Universidad del Chubut, Rawson, Chubut Argentina •University of Sydney, Sidney, New South Wales, Australia •Salud Global, Sucre, Chuquisaca, Bolivia •Universityof Chile, Santiago, Chile •Universidad Nacional de Costa Rica, Heredia, Costa Rica •Society for Emergecy and Disaster Medicine CzMA JEP, Kladno, Bohemia, Czechia •Hochschule Emden/Leer, Emden, Niedersachsen, Germany •Centro de Investigaciones de las Ciencias de la Salud - CICS- Facultad de Ciencias Médicas Universidad de San Carlos de Guatemala - USAC-,Guatemala City, Guatemala •University of

					Cagliari,CA, Italy and 11 more
56	Bioequivalence Study of Favipiravir 200 mg Film Tablet (ATABAY, Turkey) Under Fasting Conditions	Active, not recruiting	•Bioequivalence	•Drug: Favipirvir 200 mg	•Novagenix Drug R&D Center, Akyurt, Ankara, Turkey • Farmagen Ar-Ge Biyot. Ltd. Sti., Sahinbey, Gaziantep, Turkey
57	Bioequivalence Study of Favipiravir 200 mg Film Tablet (Novelfarma, Turkey) Under Fasting Conditions	Active, not recruiting	•Bioequivalence	•Drug: Test Drug 200 mg favipirvir •Drug: Referece Drug 200 mg favipirvir	•Novagenix Drug R&D Center, kyurt, Ankara, Turkey •Farmagen Ar-Ge Biyot. Ltd. Sti., Sahinbey, Gaziantep, Turkey
58	Bioequivalence Study of Favipiravir 200 mg Film Tablet (World Medicine, Turkey) Under Fasting Conditions	Not yet recruiting	•Bioequivalence	• Drug: Test: Favipirvir 200 mg (LOQLAR) •Drug: Referece: Favipirvir 200 mg (Avigan)	•Novagenix Drug R&D Center,Akyurt, Ankara, Turkey •Farmagen Ar-Ge Biyot. Ltd. Sti., Sahinbey, Gaziantep, Turkey
59	Bioequivalence Study of Lopinavir/Ritonavir 200/50 mg Film Tablet (World Medicine Ilac, Turkey) Under Fasting Conditions	Active, not recruiting	No Results Available	•Drug: Lopinavir 200Mg/Ritonavir 50Mg FT Test •Drug: Lopinavir 200Mg/Ritonavir 50Mg FT Reference	• Novagenix Drug R&D Center, Akyurt, Ankara, Turkey • Farmagen Ar-Ge Biyot. Ltd. Sti., Sahinbey, Gaziantep, Turkey

CHAPTER 3

AN EVALUATION OF CARDIOVASCULAR CLINICAL RESEARCHES IN WORLD AND TURKEY[*]

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[*]A part of this study is presented as a verbal paper presented in the 1th National Health Management Congress, Yeniyüzyıl University, Istanbul, Turkey, 7-8 December 2017

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INTRODUCTION

Clinical research; to reveal or confirm the clinical, pharmacological or other pharmacodynamic effects of one or more investigational products; identifying adverse events or reactions; to detect absorption, distribution, metabolism and excretion; studies conducted to investigate safety and effectiveness (TİTCK, 2013). These researches are designed to progressively assess whether a new drug or medicinal product candidate will be used in a larger population and these stages are named "Phase".

Each phase is designed to search for answers to specific questions for the investigational product. Each phase has a different purpose in the development of pharmaceuticals products and medicinal products and is structured according to the results of the previous phase. Phases have a process that starts with preclinical research and ends with post-clinical research. These studies are carried out within the framework of pre-determined and structured processes and this period covers an average of 10 years. These investigations are carried out in three main stages. These stages are (Ekinci, 2019);

- Pre-clinical Researches
- Clinical Researches
- Post-clinical Researches

While developing a product/molecule, it passes through these stages respectively.

A. Pre-clinical Researches (Phase 0 Researches)

Pre-clinical researches are the studies that carried out in a laboratory environment. A new molecule, a compound can be considered as search efforts. Following this phase, pre-clinical tests and invitro experiments are carried out. This stage of clinical research could be identified as Phase-0 clinical trials (Ekinci, 2019). These clinical researches are the studies that carried out in laboratory environment and on experimental animals. Laboratory studies are included preclinical tests and in-vitro experiments that the emergence of a new compound (synthesis-screening).

B. Clinical Researches

Clinical research (this phase) is carried out in four stages. These stages are;

- Phase I Clinical Researches
- Phase II Clinical Researches
- Phase III Clinical Researches
- Phase IV Clinical Researches

While Phase I Clinical Researches, Phase II Clinical Researches and Phase III Clinical Researches are done before the investigational product is licensed; Phase-IV Clinical Researches are carried out after the investigational product is licensed. In the design of the phases; the amount of the investigational product, the number of individuals, the

duration of the researches; differs in terms of to be tested the investigational product.

Phase-I Clinical Researches (Safety Researches)

It is the period of research conducted on a limited number of healthy volunteers to determine the appropriate dose range safety and toxicity of the investigational product. However, in cases where it is not possible to work on healthy volunteers such as cancer, researches can also be done on patient volunteers also.

Phase I Clinical Researches are the studies that produce hypotheses due to their nature. Phase-I clinical researches are the highest risk phase all of the clinical researches phases. For this reason, in practice it is conducted to do in two stages; namely Phase-Ia trial[13] and Phase-Ib trial in terms of safety (Ekinci, 2019).

Phase-I researches are the studies that conducted on average 20-100 volunteers to determine the safety interval of the investigational product for a year.

Phase-Ia trial is the pilot study of the clinical researches; this phase is done on volunteers between 0-20 and in the event that there are no problems in terms of safety and toxicity on the volunteers, the Phase-IIb trial is started and in this stage (the Phase-IIb trial) the number of

[13] Trial: Trial could be descriptive as a small sample of the main research/ Main research could be divided into sub-group that named trial/Sub-research is beıng the part of main researches as trial.

volunteers determined at this phase (avarage 100 volunteers) and the Phase I Clinical Research stage is completed (Ekinci, 2019).

Phase-II Clinical Researches (Safety and Effectiveness Research)

From the investigational product is the clinical research period in which the appropriate dose range, which constitutes the expected biological response, is tested by applying to a volunteer number of patients calculated according to the quality of the research in order to determine effectiveness and safety.

While the purpose of Phase-I Clinical Researches are to reveal the safety profile of the investigational product; in Phase-II Clinical Researches are aimed to prove the effectiveness of the investigational product in the disease. At this stage, it starts with the application of the best dose and method determined by the Phase-I clinical research. These period researches are the studies that produce hypotheses like Phase-I clinical researches.

In practice in terms of security, this stages could be identified in two stages as Phase-IIa trial and Phase-IIb trial (Ekinci, 2019).

Phase-IIa trial is the pilot study phase to find and prove the dose range that will affect a small number of patients. Phase-IIb trial is the stage that the investigational product determined in Phase-IIa trial is applied in more patients to optimize the dose and dose range, and to strengthen its effectiveness and safety at the level of statistical significance (Ekinci, 2019). At this stage, if it is determined that the

investigational product is beneficial in a certain amount of patients and the possible side effects are at an acceptable level, then to the next stage is passed. This period lasts an average of two years.

Phase-III Clinical Researches (Effectivness Confirmation and Monitoring of Side Effects)

At the investigational product; the effectiveness of the product and the benefit/harm ratio using the control methods such as placebo, randomized on volunteer patients, in which the therapeutic effect determined in the previous stages is applied to a wider range of patients, the effect on a new disease, different dosage ranges, methods of administration, new pharmaceutical forms are being investigated for safety.

In this period, the hypotheses of the investigational product obtained in the Phase-I Clinical Researches and Phase-II Clinical Researches are tested and the duration of the study lasts 1-5 years depending on the disease, the length of the study and the number of volunteers.

This phase also plays an important role in the approval decision for the licensing and release of the investigational product. In practice Phase-III Clinical Researches are also done in two stages Phase-IIIa trial and Phase-IIIb trial (TÜBA, 2017).

Phase-IIIa trial covers the process from the start of the research to the licensing of the investigational product. This phase also includes the process presented in the application file of the investigational product.

Phase-IIIb trial covers the period from the official authority application until the product is placed on the market. After the product is licensed, a new indication, new usage methods and methods, determination of new pharmaceutical forms, different dose trials, and a new patient population are carried out under the name of "supporting development" studies (TÜBA, 2017).

Phase-IV Clinical Researches (Long Term Safety)

The research is a wide-ranging research period after the product is licensed/permitted. In this period, it is performed on a large number of volunteer patients in order to examine the approved indications, methods of application, safety, effectiveness of their use, and to compare other products and methods used in the same treatment. Long-term side effects monitoring, pharmacoeconomic studies, quality of life studies are performed in this period.

C. Post-Clinical Researches (Scientific-Observational Researches)

Epidemiological researches are the study of the distribution and determinants of health-related events and conditions of a particular community and the use of research results to control health problems (Hayran, 2016).

Epidemiological researches are done at roughly three levels; firstly, observational descriptive research to identify health-related events and situations; secondly, analytical research based on observations, to clarify cause-effect relationships and thirdly, to finalize cause-effect

relationships and develop control methods are experimental/ intervention researches conducted (Hayran, 2016).

Epidemiological researches are the studies in which data on prescribed drugs and products are collected for larger populations and could be identified the latest phase of Phase Clinical IV researches.

Clinical researches accounts for 40% of Research and Development investments. The pharmaceutical industry is one of the most important high-tech sectors in the world in healthcare Research and Development expenditures with a volume of approximately one trillion dollars (TITCK, 2015). The pharmaceutical industry accounts for 3% of the total trade in the world and allocates an average of 15% of its turnover to Research and Development investments every year. The pharmaceutical industry spends a total of $ 70 billion on clinical research worldwide (TITCK, 2015).

Over the past decade, the effects of technological and scientific developments in the medical and health sciences have reduced the mortality rate and increased the average life span, which has led to an annual increase in world population. In the world, the death rate dropped from 2.6% in 1950s, down to 0.77% today (Ekinci & Bakır, 2015).

Deaths occur due to injuries, communicable diseases and noncommunicable diseases. In the year 2014, 55.6 million deaths happened in the world, and 37.7 million (65.2%) of these deaths were due to noncommunicable diseases. Nineteen percent of deaths caused

by noncommunicable diseases happened in the age range of 30-70 years. Cardiovascular diseases are responsible for 30.1% (17.5 million) of all deaths which corresponds to one third of all deaths, while cardiovascular diseases accounts for 44% of noncommunicable diseases related deaths (WHO, 2014a). Cardiovascular diseas take important role in noncommunicable diseases at Turkey.

Cardiovascular diseases are a group of disorders of the heart and blood vessels and they include; coronary heart diseases, cerebrovascular diseases, peripheral arterial diseases, rheumatic heart diseases, pulmonary embolism and vein thrombosis. Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. The cause of heart attacks and strokes are usually the presence of a combination of risk factors, such as unhealthy diet and obesity, physical inactivity, harmful use of alcohol tobacco, diabetes, hypertension and hyperlipidaemia (https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)). With this reasons; cardiovascular diseases are the one of the main causes of the early deaths.

Turkey Statistical Institute announced by the causes of death statistics in 2018, the share of deaths due to circulatory system diseases were

found decreased generally. The death rate caused from circulatory system diseases dropped from 39.52% in 2016s, down to 38.45% in 2018. In 2018 compared to 2016, causes of death by circulatory system diseases had decreased by 0.027 % in Turkey (see Table: 1).

Table 1: Causes of Death according to Circulatory System (%)

	2016	**2017**	**2018**	**Change**
Circulatory System	39.52	39.46	38.45	-0.027

Source: Health Statistics Yearbook, 2019

Early Death Rate[14] gives the standardized mortality rate in 100,000 population of death causes for in the age range of 30-70. According to age standardized early death rates, diseases related to the circulatory system decrease over the years. In 2018 compared to 2016, Circulatory System Diseases had decreased by 0.08 % in Turkey (see Table: 2).

Table 2: Age Standardized Early Death Rates Due to Circulatory System (Standard Population at 100,000)

	2016	**2017**	**2018**	**Change**
Circulatory System Diseases	122.76	120.79	113.35	-0,08

Source: Health Statistics Yearbook, 2019

* In the study mortality rates were standardized to age using the World Standard Population.

[14]While calculating age-standardized mortality rates, the World Standard Population determined by WHO and the European Standard Population determined by EUROSTAT were used. These standard populations weigh the populations and deaths in the age groups, making the age pattern similar for all countries. Thus, comparisons between countries can be made in a healthier way by preventing the differences caused by the age structure of the population. Detailed information for the world and European standard population can be found in the links below.

In 2018 compared to 2016, Ischemic Heart Diseases, Myocardial Infarction, Cerebrovascular Diseases decreased in Turkey (respectively 0.11%; 0.09; 0.12) (see Table: 3).

Table 3: Age Standardized Early Death Rates Due to Circulatory System (Standard Population at 100,000)

	2016	**2017**	**2018**	**Change**
Ischemic Heart Disease	60.59	58.98	54.18	-0,11
Myocardial Infarction	42.57	40.54	38.79	-0,09
Cerebrovascular Disease	25.13	24.10	22.02	-0,12

Source: Health Statistics Yearbook, 2019
* Mortality rates were standardized to age using the World Standard Population.

Although the share of cardiovascular diseases in early deaths and deaths decreases by years, still it has an important place among the causes of death. Global action plan for the prevention and control of noncommunicable diseases determined by WHO[15]. In this study policy actions for prevention of major noncommunicable diseases are listed under objective 3 and for the purpose of to preventetion to cardiovascular diseases are listed as follows (WHO, 2013):

- Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke

[15] Global action plan for the prevention and control of noncommunicable diseases 2013-2020; Scope of this plan: the action plan provides a road map and a menu of policy options for all Member States and other stakeholders, to take coordinated and coherent action, at all levels, local to global, to attain the nine voluntary global targets, including that of a 25% relative reduction in premature mortality from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases by 2025 (WHO, 2014b).

and to persons with high risk (≥ 30%) of a fatal and nonfatal cardiovascular event in the next 10 years

- Acetylsalicylic acid for acute myocardial infarction
- Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke, and to persons with moderate risk (≥ 20%) of a fatal and nonfatal cardiovascular event in the next 10 years
- Detection, treatment and control of hypertension and diabetes, using a total risk approach
- Secondary prevention of rheumatic fever and rheumatic heart disease
- Acetylsalicylic acid, atenolol and thrombolytic therapy (streptokinase) for acute myocardial infarction
- Treatment of congestive cardiac failure with ACE inhibitor, beta-blocker and diuretic
- Cardiac rehabilitation post myocardial infarction
- Anticoagulation for medium-and high-risk non-valvular atrial fibrillation and for mitral stenosis with atrial fibrillation
- Low-dose acetylsalicylic acid for ischemic stroke
- Very cost-effective i.e. generate an extra year of healthy life for a cost that falls below the average annual income or gross domestic product per person.

- A 25% relative reduction in overall mortality from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases
- At least 50% of eligible people receive drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes
- A 25% relative reduction in the prevalence of raised blood pressure or contain the prevalence of raised blood pressure, according to national circumstances (WHO, 2013).

A comprehensive approach in cardiovascular diseases is required in to improve the preventive and treatment performance. This approach is based on essential technologies (e.g. blood pressure measurement, blood sugar and cholesterol measurement devices with strips, weighing scales, urine strips for albumin, pacemakers, prosthetic valves, and patches for closing holes in the heart) and medicines (e.g. aspirins, statins, angiotensin-converting enzyme inhibitor, thiazide diuretics, beta-blocker, long acting calcium-channel blocker, insulin). At the same time, it is necessary to monitor the cardiovascular risk factors and to apply early diagnosis and treatment in order to control the cardiovascular diseases. In this context, serious studies related circulatory system and cardiovascular diseases are done in Turkey. One of this study is "The Distribution Of The Main Diseases/Health Problems Experienced By İndividuals Aged 15 And Over İn The Last 12 Months İn 2016".

In a study on the distribution of the main diseases/health problems experienced by individuals aged 15 and over in the last 12 months in 2016;

- Total hypertension rate had a share of 15.8%; and it had been determined that it was high rate in women.
- Total Arthrosis rate had a share of 7.7% and it had been determined high in women.
- Total Coronary Heart Disease (angina, chest pain, spasm) rate had a share of 6.5% and it had been determined high in women.
- Myocardial Infarction (heart attack) rate had a share of 2.1%; the ratio of males were slightly higher than females.
- Stroke-Paralysis (brain hemorrhage, cerebral thrombosis) rate had a share of 0.9%; the ratio of males were slightly higher than females.

Table 4: Cardiovascular Disease/Health Problems Experienced by 15 and Over Individuals in the Last 12 Months, (%) 2016

	Woman	**Man**	**Total**
Hypertension	20.5	11.1	15.8
Arthrosis	10.5	4.9	7.7
Coronary Heart Disease (Angina, Chest Pain, Spasm)	7.1	5.9	6.5
Myocardial Infarction (Heart Attack)	2.0	2.1	2.1
Stroke-Paralysis (Brain Hemorrhage, Cerebral Thrombosis)	0.8	1.0	0.9

Source: Health Statistics Yearbook, 2019

Number of patients diagnosed with hypertension and high cholesterol in the last 12 months in individuals in the age range of 15 and over in

2017 is 7.1% and 4.8% respectively. The number of patients diagnosed with hypertension and high cholesterol at any given time (prevalence) is 16.2% and 10.1%. respectively (Başara et all, 2019).

The Ministry of Health of Turkey Household Health Survey in 2017 at in the age range of 15 and older individuals; for total cholesterol in individuals;

- The rate of total cholesterol with 190 mg/dl and above is 24.7%; the rate of total cholesterol with 240 mg/dl and above is 8.0% was found.
- At the same survey; at in the age range of 15 and older individuals for triglyceride levels; the rate of triglyceride 150mg/dl and above is 25.6%; the rate of triglyceride 180 mg/dl and above is 16.7% was found (Başara et all. 2019).

Targeted screening for total cardiovascular risk, with blood glucose testing and blood pressure and cholesterol measurement, is more cost effective than screening the whole population, and is more likely to identify individuals at high cardiovascular risk, for lower cost (WHO, 2014).

Individuals high cholesterol and trigliserid levels provide important information in terms of frequency of cardiovascular diseases. In cardiovacular diseases, drugs for preventive and therapeutic treatment are used in individuals. For this concepts; Anatomical Therapeutic Chemical (ATC) is a drug classification system that is supported, managed and developed by the World Health Organization (WHO).

ATC divides the drugs into different groups according to their structural or therapeutic, pharmacological, chemical and chemical compound properties with their effective organs or systems. The ATC Code of the cardiovascular system is identified by "C". It is coded as Antihypertensives C02, Diuretics C03, Beta Blocking Agents C07, Calcium Channel Blockers C08, Drugs Effective on the Renin-Angiotensin System C09, Lipid Modifying Agents C10. Defined Daily Dose (DDD) is the daily maintenance dose used in adults for the main indication of a drug in the ATC system. In the study of international comparison of daily drug consumption amount per thousand people; Defined Daily Dose was found 187.7 in Turkey, 451.3 in OECD countries at 2017.

In the study of international comparison of daily antihypertensive drug consumption amount per thousand people; for Turkey Defined Daily Dose was found 95 in 2008 and 149 in 2017.

In the study of international comparison of daily cholesterol lowering drug (ATC-C10) consumption amount per thousand people; for Turkey Defined Daily Dose was found 18 in 2008 and 24 in 2017.

Table 5: Information on Cardiovascular System Drugs

	2013	**2014**	**2015**	**2016**	**2017**	**Change**
Pharmaceutical Sales Volume, Million Box	185.2	191.4	203.7	212.8	225.9	0.2198
Daily Drug Consumption Amount per 1000 People, DDD	158.9	160.8	165.4	167.4	176.4	0.1101
Pharmaceutical Sales Value, Million ₺	1,389.4	1,434.6	1,541.6	1,744.0	2,133.3	0.5354

Source: Health Statistics Yearbook, 2019

While the sales volume of drugs belonging to the cardiovascular system was 185.2 million boxes in 2013; it had been 238.3 million boxes in 2017. In 2017 compared to 2013, cardiovascular pharmaceutical sales volume (million box) had increased by 21.9% in Turkey.

In the study of international comparison of daily cardiovascular system drug consumption amount per thousand people; Defined Daily Dose was found 158.9 in 2008 and 176.4 in Turkey. In 2017 compared to 2013, cardiovascular system drug consumption amount per thousand people; for Turkey Defined Daily Dose had increased by 11%. While the value of sales of drugs used in cardiovascular system in Turkey was 1,389.4 million pounds in 2013 and this value was 2,133.3 million lira in 2017. In 2017 compared to 2013, the value of sales of drugs used in cardiovascular system had increased by 53.5%.

In addition to all these data, various studies on cardiovascular diseases are conducted in World. The most important of these studies is the Global Burden of Diseases. Global Burden of Diseases Study is a global study to evaluate the health profile and changes in health profile of 195 countries, 21 regions and 7 super regions. With this study, some calculations are made that classify health. The main calculations are Disability Adjusted Life Year (DALY), Lost Life Year (YLL), HALE etc.

Disability Adjusted Life Year is an absolute measure of health loss that does not result in deaths at an early age but counts the years lost due to diseases and injuries leading to long-term loss of function. 1 (one) DALY refers to 1 (one) year of healthy life. YLL is expressed as the year of life lost due to early death.

Table 6: Change of the YLL-DALY Reasons in 2002-2017, Turkey

		2002	2017	Change (%)
YLL	**Ischemic Heart Disease**	1,507,528	1,509,976	0.16
	Stroke	413,194	642,929	55.60
DALY	**Ischemic Heart Disease**	1,556,352	1,577,224	1.34
	Stroke	520,813	819,523	57.35

Source: Health Statistics Yearbook, 2019

In this study, for the reason of Year Of Life Lost; ischemic heart diseases (16%) and stroke (55.60%) increased at 15 years. While ischemic heart disease increased by 24% in men; it decreased by 2% in women for 15 years. For stroke; it increased 100% in men and 19.97% in women for 15 years.

In this study, for the reason of Disability Adjusted Life Year; ischemic heart diseases (1.34%) and stroke increased (57.35) at 15 years. While ischemic heart disease increased by 1.05% in men and by 1.98% in women. For stroke; it increased by 93.10% in men and by 30% in women.

Due to the morbidity and mortality rates caused by cardiovascular diseases and the drugs used in their treatments, they contain significant burdens in the country's economies. So, to reduce

cardiovascular diseases and deaths, efforts are required to make progress on using medicines and basic technologies. And in this progress, it is important to develop research and develeopment activities in cardiovascular systems treatments (e.g. medicines/medical devices). Therefore, there is a need for information on research and development activities in the cardiovascular field.

The study aimed to determine current status of the clinical researches and cardiovascular clinical researches in world and Turkey. Clinical trials data are taken from clinicaltrials.gov.tr[16]. With the heading "Cardiovascular Diseases", clinicaltrials.gov.tr was searched and the data in this field were analyzed. This study is a descriptive and cross-sectional study. The data were made on the current data in the www.clinicaltrial.gov.tr. and recorded on 21 February 2017 were analyzed.

Clinical researches in the study was carried out under two main titles as "total clinical studies" and "cardiovascular clinical studies". Clinical studies, which are handled under two main titles, were also examined in detail to their "phases, gender and age". Total clinical trials give the number of clinical trials conducted worldwide.

The total number of clinical trials and the number of clinical trials to age, gender, and phases differ. This situation is thought to result from

[16] "Clinicaltrials.gov.tr" is a record of clinical trials. It is operated by the National Library of Medicine, the National Institute of Health of the United States, and is the largest clinical research database from 209 countries (wikipedia)

the same clinical research being applied differently according to gender and age.

In the following sections of the study, the current status of clinical trials and cardiovascular clinical trials, distribution by phases, gender and age were detailed.

CLINICAL TRIALS

257,931 clinical trials were conducted in the World in 2017. 84% of these clinical trials made in Americas (64%) and European countries (20%). 16% of clinical trials were made by Canada (%5), Middle East (%3), East Asia (%3), Pasificia (%3) (see Chart1).

Table 7: Clinical Trials, 2017

	Clinical Trials	**Cardiovascular Clinical Trials**
World	257931	31470
Turkey	2677	143

In 2017, a total of 2,677 clinical trials were conducted in Turkey and the share of Turkey's total clinical trials in the world was 1%.

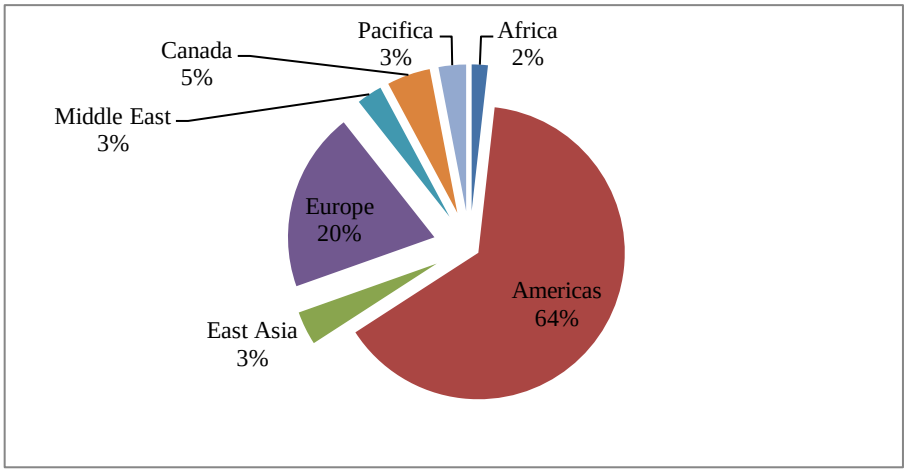

Chart 1: Total Clinical Trials by Region, World 2017

31,470 cardiovascular clinical trials have been conducted in the World and this rate was corresponded to 12,2% of the total clinical research conducted in the world. In addition, 88% of these studies are conducted in America (54%), Europe (23%) and Asia (11%) (see Chart 2).

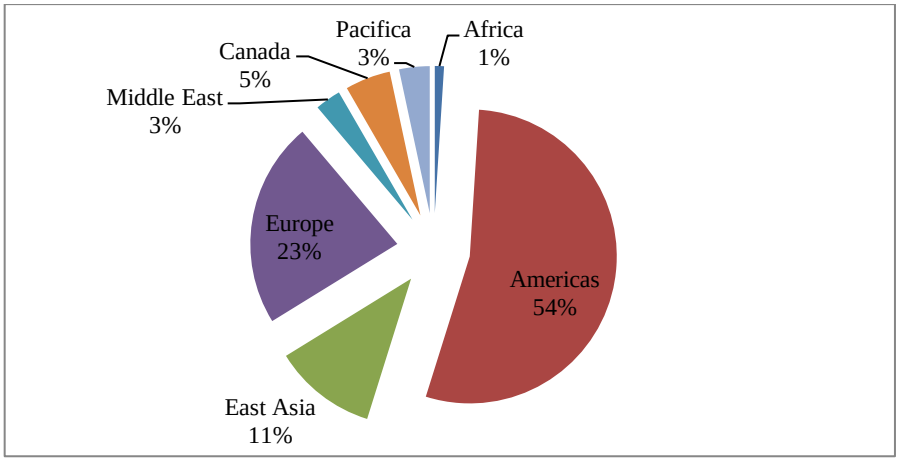

Chart 2: Cardiovascular Clinical Trials according to Region, World 2017

The distribution of clinic trials according to phases in the world, Phase 2 trials with 35% take the first place and this was followed by Phase 1 and Phase 3 studies, respectively (see Chart 3).

Table 8: Clinical Trials according to Phase, 2017

	Clinical Trials World	Cardiovascular Clinical Trials World	Turkey	Cardiovascular Clinical Trials Turkey
Early Phase 1	2181	213	13	0
Phase 1	36405	2573	36	2
Phase 2	51875	5035	263	15
Phase 3	32428	4030	944	97
Phase 4	24020	3845	438	29

Early phase studies were constituted a very low rate, like 2% of total trials (see Chart 3).

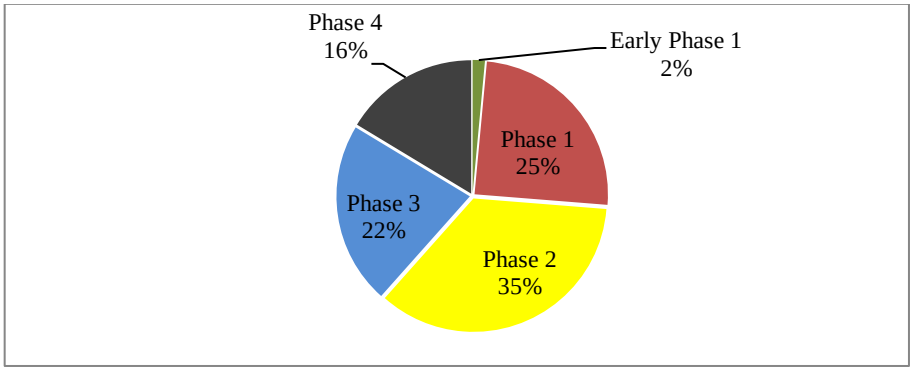

Chart 3: Distribution of Clinical Trials according to Phases, World 2017

The distribution of clinic trials according to phases in the Turkey, Phase 3 trials with 56% take the first place and this was followed by Phase 4 and Phase 2 trials, respectively. Early phase trials were constituted a very low rate, like 1% of total trials (see Chart 4).

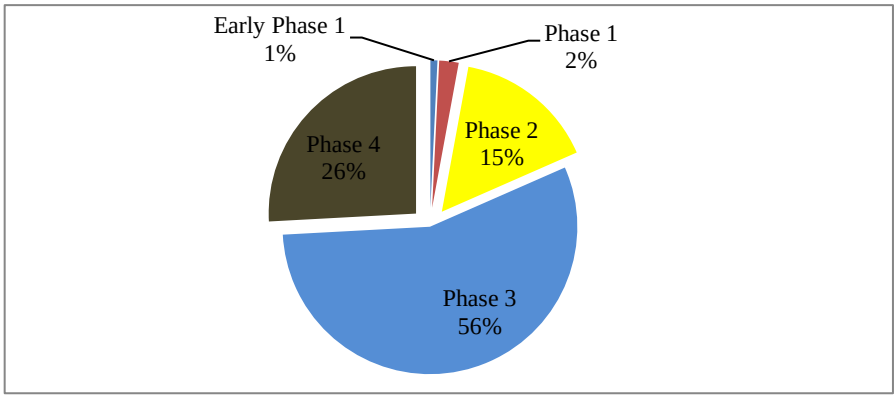

Chart 4: Clinical Trials according to Phases, Turkey 2017

The distribution of cardiovascuar clinic trials according to phases in the world, Phase 2 trials with 32% take the first place and this was followed by Phase 3 and Phase 4 trials, respectively. In the total trials the rate of Phase 1 trials share in 16% and Early Phase trials share 1% (see Chart 5).

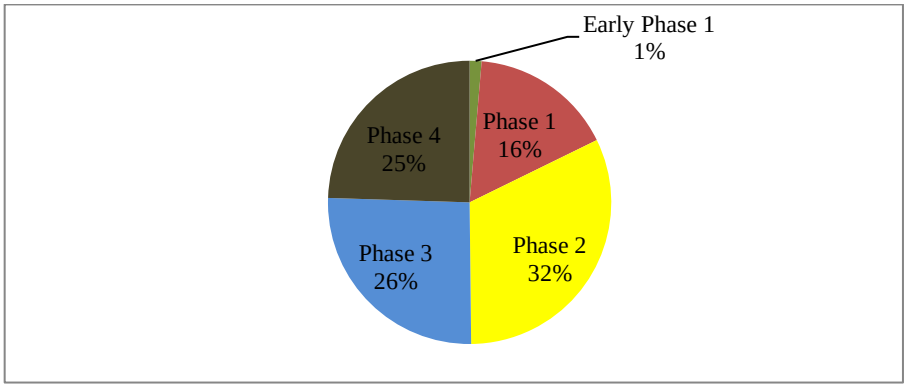

Chart 5: Cardiovascular Clinical Trials according to Phases, World 2017

The distribution of cardiovascular clinic trials according to phases in the Turkey, Phase 3 trials with 68% take the first place and this was followed by Phase 4 and Phase 2 trials, respectively. In the total trials the rate of Phase 1 and Early Phase trials share in 1% (see Chart 6).

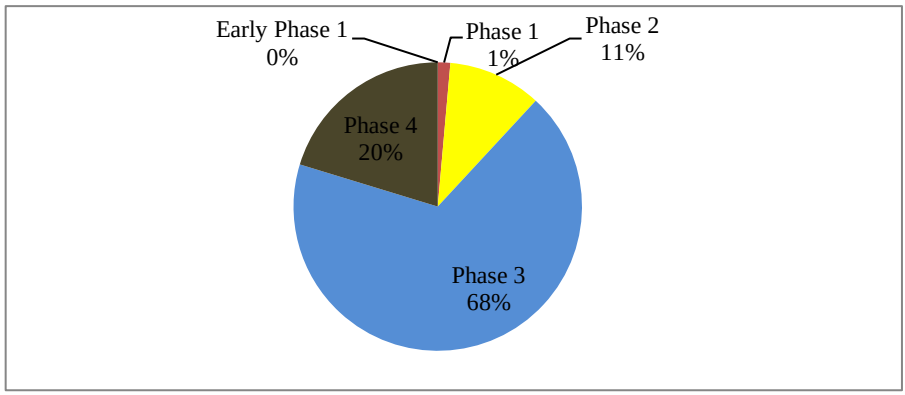

Chart 6: Cardiovascular Clinical Trials according to Phases, Turkey 2017

CLINICAL TRIALS ACCORDING TO GENDER

In this section, total clinical trials and cardiovascular clinical trials current status were evaluated according to gender in the world and Turkey; calculated values are given in Table 9.

Table 9: Distribution of Clinical Trials according to Gender, 2017

	Clinical Trials World	Cardiovascular Clinical Trials World	Clinical Trials Turkey	Cardiovascular Clinical Trials Turkey
Female	173942	15372	2555	142
Male	166029	15413	2321	138

The distribution according to gender of clinical trials in the world and Turkey were close to each other as numerical value between men and women. In the cardiovascular clinical trials by gender the same feature was evaluated also.

Clinical Trials according to Female

In this section, total clinical trials and cardiovascular clinical trials current status were evaluated according to female groups in the world and Turkey and the calculated values are given in this section.

Table 10: Distribution of Clinical Trials according to Female, 2017

	Clinical Trials World	Cardiovascular Clinical Trials World	Turkey	Cardiovascular Clinical Trials Turkey
Early Phase 1	2039	206	12	0
Phase 1	32366	2441	30	0
Phase 2	49533	4982	251	7
Phase 3	31330	3969	895	48
Phase 4	23229	3774	413	21

Total Clinical Trials according to Female

In female group 36% Phase 2 trials are conducted in the world and followed by phase 1 trials and phase 3 trials (23%). In the total clinical trials in female the rate of Early Phase 1 trials share in 1%.

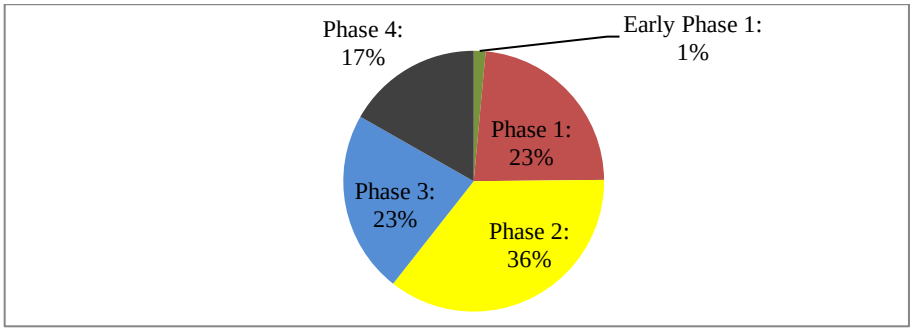

Chart 7: Clinical Trials according to Female, World 2017

In female group 56% Phase 3 trials are conducted in Turkey and followed by phase 4 trials and phase 2 trials (respectively 26%; 15%). In the total clinical trials in female the rate of Phase 1 was 2% and Early Phase 1 trials share in 1% in Turkey (see Chart 8).

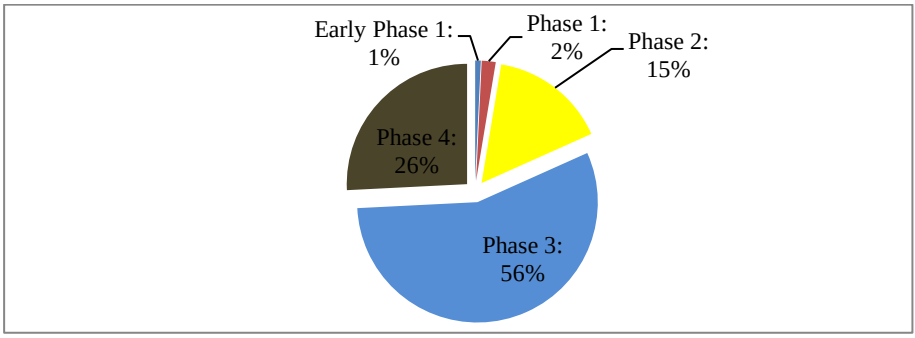

Chart 8: Clinical Trials according to Female, Turkey 2017

Cardiovascular Clinical Trials according to Female

In female group 32% Phase 2 cardiovascular clinical trials are conducted in the world and followed by phase 3 trials and phase 4 trials (respectively 26%; 25%). In the cardiovascular clinical trials in female the rate of Phase 1 trials was 16% and Early Phase 1 trials share in 1% in the World (see Chart 9).

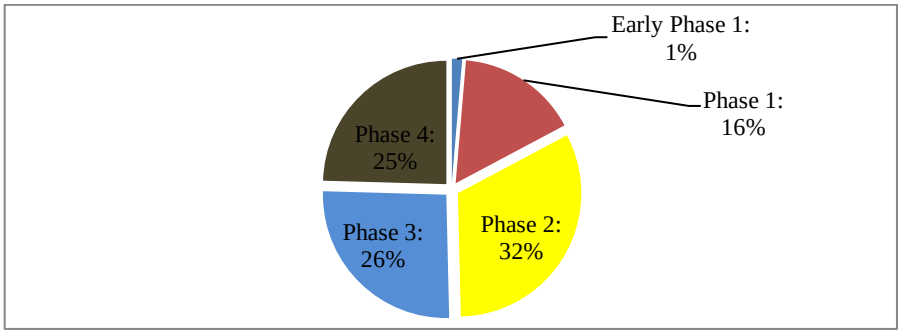

Chart 9: Cardiovascular Clinical Trials according to Female, World 2017

In female group 63% Phase 3 cardiovascular clinical trials are conducted in Turkey and followed by phase 4 trials and phase 2 trials (respectively 28%; 9%). In Turkey Early Phase 1 cardiovascular trials and Phase 1 cardiovascular trials were not conducted (see Chart 10).

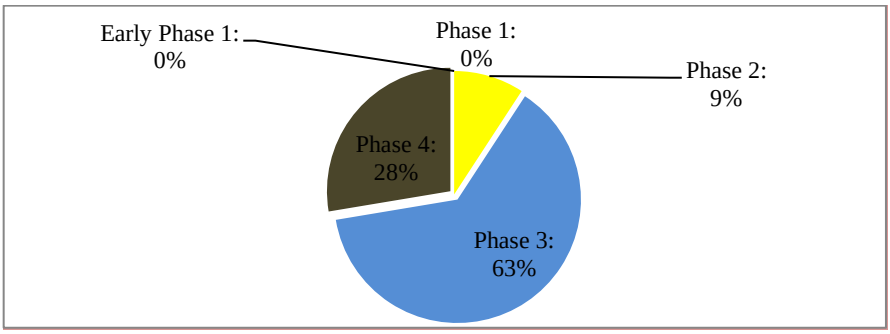

Chart 10: Cardiovascular Clinical Trials according to Female, Turkey 2017

Clinical Trials according to Male

In this section, total clinical trials and cardiovascular clinical trials current status were evaluated according to Male groups in the World-Turkey and also calculated values are given in this section.

Table 11: Distribution of Clinical Trials according to Male, 2017

	Clinical Trials World	Cardiovascular Clinical Trials World	Turkey	Cardiovascular Clinical Trials Turkey
Early Phase 1	1916	208	11	0
Phase 1	34285	2563	31	1
Phase 2	47050	4947	236	8
Phase 3	29186	3948	890	48
Phase 4	21712	3747	390	20

Total Clinical Trials according to Male

In male group 35% Phase 2 trials are conducted in the world and followed by phase 1 trials, phase 3 and phase 4 trials (respectively 26%; 22%; 16%). In the total clinical trials in male the rate of Early Phase 1 trials share in 1% (see Chart 11).

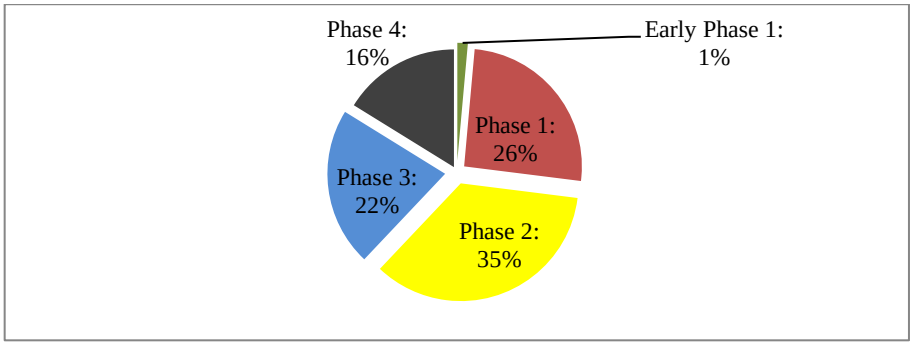

Chart 11: Clinical Trials by Male, World 2017

In male group 57% Phase 3 trials are conducted in Turkey and followed by phase 4 trials and phase 2 trials (respectively 25%; 15%). In the total clinical trials in male group the rate of Phase 1 was 2% and Early Phase 1 trials share in 1% in Turkey (see Chart 12).

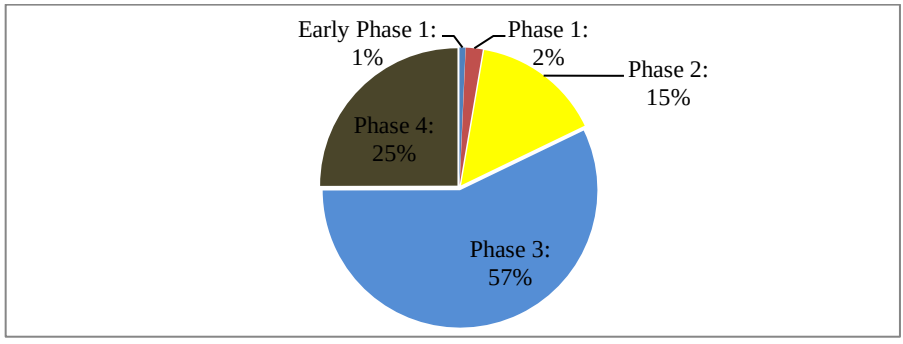

Chart 12: Clinical Trials by Male, Turkey 2017

Cardiovascular Clinical Trials according to Male

In male group 32% Phase 2 cardiovascular clinical trials are conducted in the world and followed by phase 3, phase 4 and phase 1 trials (respectively 26%; 24%; 17%). In the cardiovascular clinical trials in the male group the rate of Phase 1 was 17% and Early Phase 1 trials share in 1% in the World (see Chart 13).

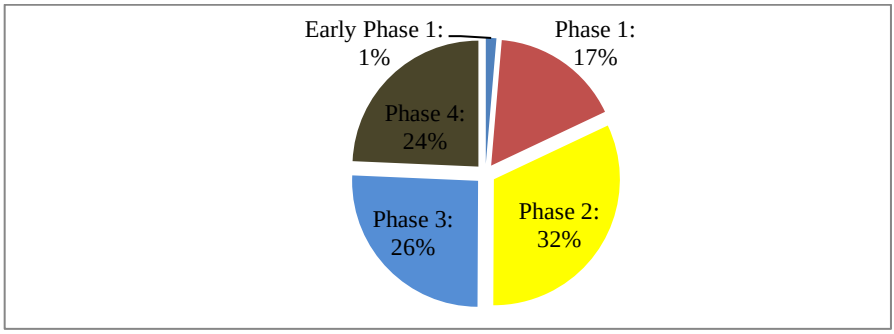

Chart 13: Cardiovascular Clinical Trials according to Male, World 2017

In male group 62% Phase 3 cardiovascular clinical trials are conducted in Turkey and followed by phase 4, phase 2 trials respectively 26%; 11% (see Chart 14).

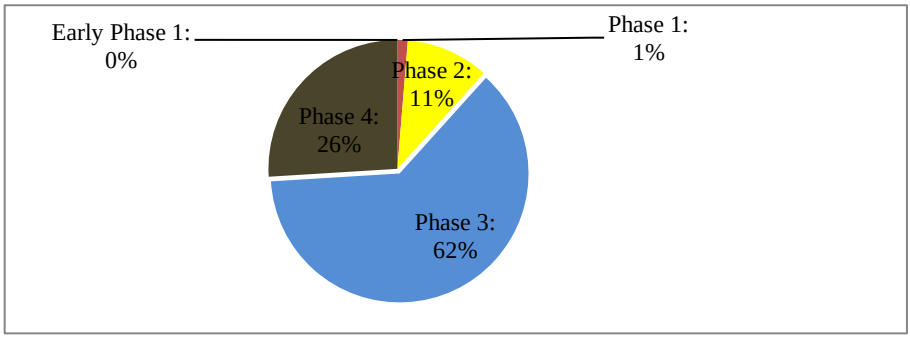

Chart 14: Cardiovascular Clinical Trials according to Male, Turkey 2017

In Turkey cardiovascular clinical trials in the male group the rate of Phase 1 was 1% but Early Phase 1 cardiovascular clinical trial was not conducted in Turkey (see Chart 14).

CLINICAL RESEARCHES TO AGE GROUPS

In this section, total clinical trials and cardiovascular clinical trials current status were evaluated according to age in the world and Turkey and also calculated values are given in this section.

Table 12: Distribution of Clinical Trials according to Age, 2017

Age	Clinical Trials,World	Cardiovascular Clinical Trials World	Clinical Trials Turkey	Cardiovascular Clinical Trials Turkey
Birth-17	13834	1769	637	17
18-65	138501	15190	2410	132
66 and upper	101567	13834	1712	124

55% of the clinical trials were conducted in the world is in the age range of 18-65, 40% in the age range of 66 and upper age, 5% in the age range of birth-17 (see Chart 15).

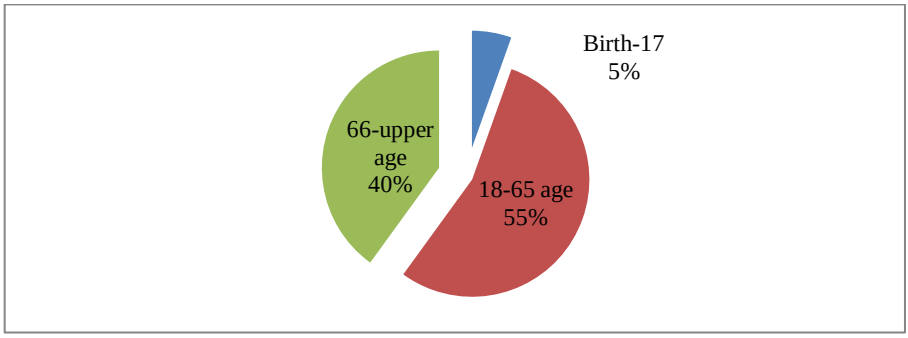

Chart 15: Total Clinical Trials according to Age, World, 2017

51% of the clinical trials were conducted in the Turkey is in the age range of 18-65, 36% in the age range of 66 and upper age, 13% in the age range of birth-17 (see Chart 16).

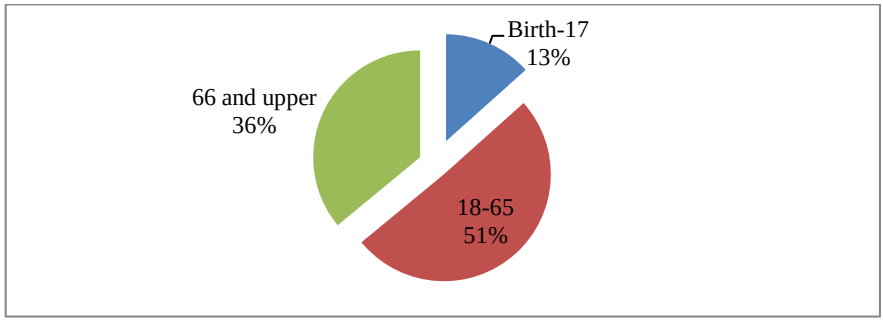

Chart 16: Total Clinical Trials according to Age, Turkey, 2017

49% of the cardiovascular clinical trials were conducted in the world is in the age range of 18-65, 45% in the age range of 66 and upper age, 6% in the age range of birth-17 age group (see Chart 17).

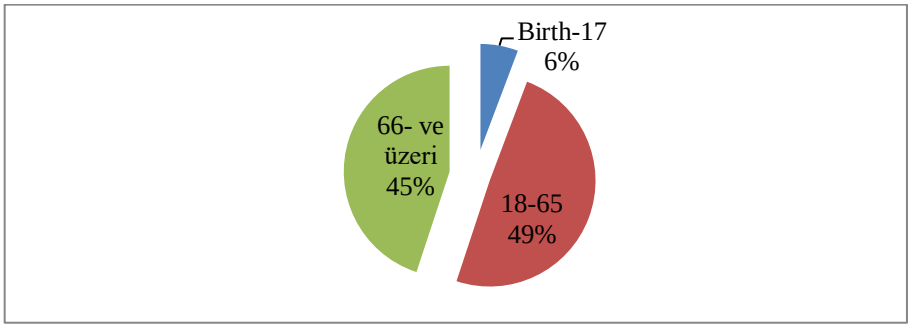

Chart 17: Cardiovascular Clinical Trials according to Age, World, 2017

48% of the cardiovascular clinical trials were conducted in Turkey is in the age range of 18-65 age group, 46% in the age range of 66 and upper age, 6% in the age range of birth-17 age group (see Chart 18).

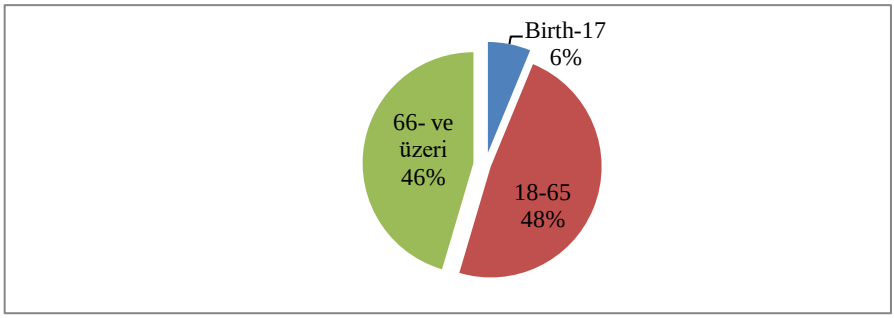

Chart 18: Cardiovascular Clinical Trials according to Age, Turkey 2017

In the evaluation of the distribution of total clinical trials according to phases and age groups were given Table 13. According to table;

Table 13: Total Clinical Trials according to Age and Phase, 2017

Phase	Age	Clinical Trials World	Cardiovascular Clinical Trials World	Turkey	Cardiovascular Clinical Trials Turkey
Early Phase 1	Birth-17	353	33	3	0
	18-65	2066	207	13	0
	66 and upper	1353	168	7	0
Phase 1	Birth-17	4303	299	9	0
	18-65	35207	2478	32	1
	66 and upper	20906	2078	20	1
Phase 2	Birth-17	8626	622	60	1
	18-65	49365	4873	235	7
	66 and upper	38871	4450	192	7
Phase 3	Birth-17	7375	503	209	2
	18-65	29566	3861	862	47
	66 and upper	23735	3605	758	48
Phase 4	Birth-17	4186	312	77	2
	18-65	22297	3771	389	9
	66 and upper	16702	3533	229	18

- Phase 2 and Phase 3 clinical trials were the most frequently studied phase in the age range of birth and 17 age,

- Phase 2 and Phase 1 clinical trials were studied in the age range of 18-65,
- Phase 2 and Phase 3 clinical trials were studied in the age range of 66 and upper age (see Chart 19).

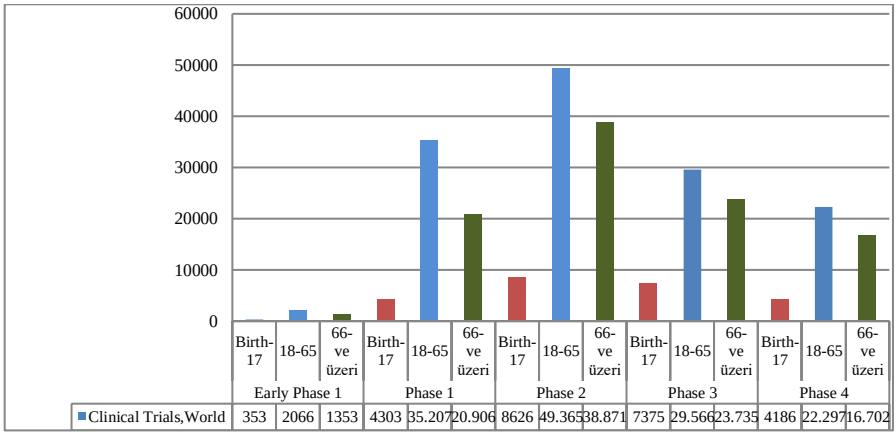

Chart 19: Total Clinical Trials according to Phase and Age, World 2017

In the evaluation of the distribution of total clinical trials according to phases and age groups in Turkey;

- Phase 3 and Phase 4 clinical trials were the most frequently studied phase in the age range of birth and 17 age,
- Phase 3 and Phase 4 clinical trials were studied in the age range of 18-65,
- Phase 3 and Phase 4 clinical trials were studied in the age range of 66 and upper age (see Chart 20).

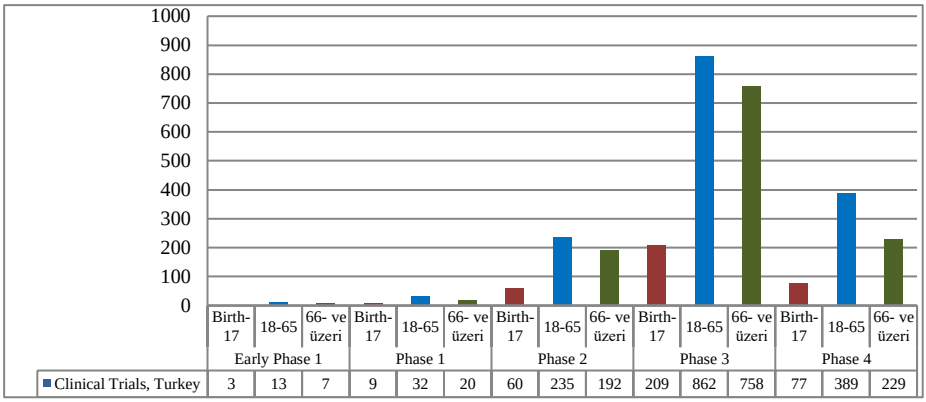

Chart 20: Total Clinical Trials according to Phase and Age, Turkey 2017

In the evaluation of the distribution of cardiovascular clinical trials according to phases and age groups in the world;

- Phase 2 and 3 cardiovascular clinical trials were the most frequently studied phase in the age range of birth and 17 age,
- Phase 2, Phase 3 and Phase 4 cardiovascular clinical trials were studied in the age range of 18-65,
- Phase 2, Phase 3 and Phase 4 cardiovascular clinical trials were studied in the age range of 66 and upper age (Chart 21)

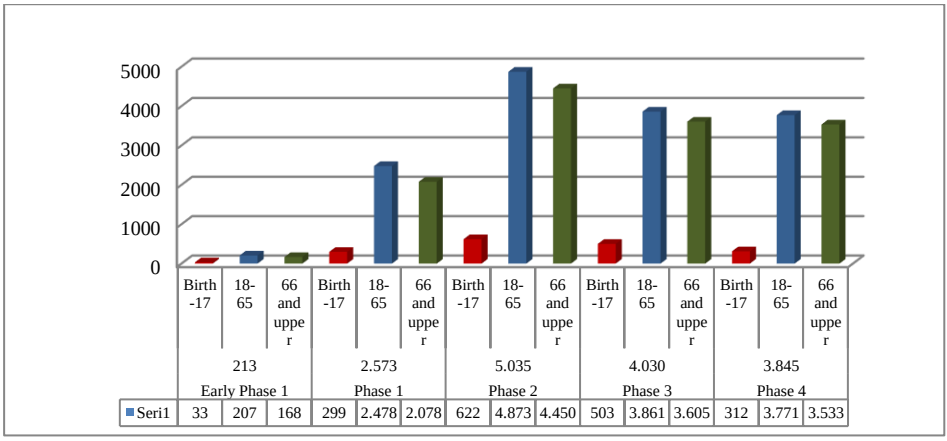

Chart 21: Cardiovascular Clinical Trials according to Phase - Age, World 2017

In the evaluation of the distribution of cardiovascular clinical trials according to phases and age groups in Turkey;

- Phase 3 and Phase 4 clinical trials were studied in the age range of birth and 17 age,
- Phase 3 cardiovascular clinical trials were studied in the age range of 18-65,
- Phase 3 and Phase 4 cardiovascular clinical trials were studied in the age range of 66 and upper age (see Chart 22)

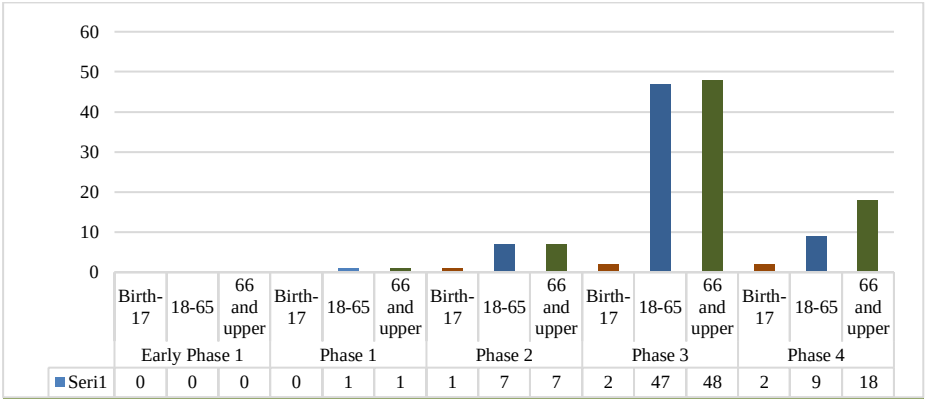

Chart 22: Cardiovascular Clinical Trials according to Phase- Age, Turkey 2017

CONCLUSIONS

The highest share in total clinical research in the world was Americas, than European countries were in the second place. Turkey's share in the world received from clinical trials was found to be 1%.

- America takes the highest share in cardiovascular clinical trials in the world; followed by European and Asian countries.

- The ratio of cardiovascular clinical trials in total clinical trials in the world was 12.2%

The ratio of Turkey's cardiovascular clinical trials to the total cardiovascular clinical trials in the world was found 0.46% indicating Turkey had a very low share at cardiovascular trials.

And also the ratio of Turkey's cardiovascular clinical trials in the total cardiovascular clinical trials in Turkey was found 5.64%.

However, since this ratio is 12.2% in the world; Turkey's cardiovascular clinic trials share in the world can easily be doubled.

- In clinical trials conducted in the world, early phase 1 clinical trials are 1%, however, it was determined that the total phase 1 clinical trials corresponded to ¼ of the total clinical trials in the world. At the same time clinical trials that was conducted in the world, Phase 2 clinical trials had the most share in the total clinical trials.
- In Turkey Phase 3 and Phase 4 clinical trials were conducted mostly. The ratio of Turkey's Phase 1 clinical trials in the total clinical trials in Turkey was found 2.9% and it was very low compared to the world scale.
- In cardiovascular clinical trials conducted in the world, Phase 1 clinical trials have 18% share, and at the same time in cardiovascular clinical trials in the world, phase 2 cardiovascular clinical trials had the most share.
- In Turkey Phase 3 cardiovascular clinical trials was conducted mostly.

- The ratio of Turkeys' Phase 1 cardiovascular clinical trials in the total cardiovascular clinical trials that conducted in Turkey was calculated 1.4% and this result shows that Turkeys' Phase 1 cardiovascular clinical trials are at a very low level compared to the world scale.
- The distribution of clinical trials according to gender in the world and Turkey were close to each other as numerical value between men and women. In the cardiovascular clinical trials by gender the same feature was also evaluated.
- In women group; in total trials Phase 2 trials conducted had a share of 36% mostly in world; Phase 3 trials conducted had a share of 56% in Turkey.
- In men group; in total trials Phase 2 trials conducted had a share of 35% mostly in world; Phase 3 trials conducted had a share of 57% in Turkey.
- In women group; in cardiovascular trials, Phase 2 trials conducted had a share of 32% mostly in world; Phase 3 trials conducted had share of 63% in Turkey.
- In men group; in cardiovascular trials, Phase 2 trials conducted had a share of 32% mostly in world; Phase 3 trials conducted had a share of 62% in Turkey.
- 95% of clinical researches in the world are carried out with adults and in Turkey 87% of clinical researches are carried out with adults.

- 94% of cardiovascular trials, in the world are carried out in adults and in Turkey 94% of clinical researches are carried out with adults.
- In the distribution of the phases according to age groups in total clinical research;

In the age range of 0-17, Phase 2 and phase 3 clinical trials were the most frequently studied phase; in the age range of 18-65, Phase 2 and phase 1clinical trials were studied; in the age range of 66 and upper age, Phase 2 and phase 3 clinical trials were studied in the world.

- In the distribution of the phases according to age groups in total clinical research in Turkey;

In the age range of 0-17, Phase 3 and Phase 4 clinical trials were the most frequently studied phase; in the age range of 18-65, Phase 3 and Phase 4 clinical trials were studied; in the age range of 66 and upper age, Phase 3 and Phase 4 clinical trials were studied.

- In the distribution of cardiovascular clinical trials according to phases and age groups in the world;

In the age range of 0-17 years, Phase 2 and Phase 3 cardiovascular clinical trials were the most frequently studied phase; in the age range of 18-65, Phase 2, Phase 3 and Phase 4 cardiovascular clinical trials were studied; in the age range of 66 and upper age, Phase 2, Phase 3 and Phase 4 cardiovascular clinical trials were studied.

- In the distribution of cardiovascular clinical trials according to phases and age groups in Turkey;

In the age range of 0-17, Phase 3 and Phase 4 clinical trials were studied; in the age range of 18-65, Phase 3 cardiovascular clinical trials were studied; in the age range of 66 and upper age, Phase 3 and Phase 4 cardiovascular clinical trials were studied.

While 84% of total clinical trials made in Americas and European countries; 77% of cardiovascular clinical researches are conducted in Americas and Europe. Turkey conducted 1% of total clinical trials and 0.46% of cardiovascular clinical researches are conducted in Turkey. Beside this; cardiovascular clinical trials have been conducted in the Worlds' rate was corresponded to 12,2% of the total clinical trials conducted in the world. So Turkey increased its cardiovascular clinical trials' share in the total cardiovascular clinical trials 4-5 times at least.

In the evaluation according to gender, it was determined that the phases are distributed in a balanced level in total clinical trials and that there is no difference between men and women in this distribution. However, there are differences in the distribution of the total phase of clinical trials in Turkey and this distribution did not differ between men and women.

In the evaluation according to gender, it was determined that the phases are distributed in a balanced level in cardiovascular clinical trials and that there is no difference between men and women.

However, there are differences in the distribution of the total phase cardiovascular clinical trials in Turkey and this distribution did not differ between men and women.

In the evaluation according to gender, we can conclude that phase studies in the cardiovascular field are performed similarly among men and women, therefore, gender is not an important factor in the phase studies conducted in the cardiovascular field.

In the evaluation according to age, it was determined that clinical trials are conducted out on adults mostly and the same is true for cardiovascular clinical trials (for world and Turkey).

Since it is determined that the clinical studies are concentrated in the phase 2 and 3 studies and in the age range of 18-65, it can be said that a more innovative drug group can be reached in the treatments for cardiovascular diseases in the following years, but new clinical studies are needed in the long term according to the phase 1 and Early phase 1 studies.

No data from Phase 0 studies are available in the clinical trial. Therefore, it makes it difficult to evaluate the data of clinical research in an integrated way (From Phase 0 clinical researches to Epidemiological researches). Early Phase I trials rate in Turkey is 0.59% in the total early phase I clinical trials; and there is no early phase I trials conducted in cardiovascular research. Phase I trials rate

in Turkey is 0,099% in the phase I clinical trials; and in cardiovascular Phase I trials in Turkey's rate was 0.077%.

Turkey has serious legal regulations regarding clinical trials compatible with international regulations. Turkey has Phase I Clinical Research Centers approved by legal regulations and could use capacities (in the centers) effectively in Phase I trials[17]. Phase II trials rate in Turkey is 0.5% in the total phase II clinical trials; and in cardiovascular Phase II trials in Turkey'a rate was 0.29%. Phase III trials rate in Turkey was 2.9% in the total phase III clinical trials; and in cardiovascular Phase III trials in Turkey's rate was 2.4%. Phase IV trials rate in Turkey was 1.8% in the total phase IV clinical trials; and in cardiovascular Phase IV trials in Turkey's rate was 0.75%. To the other phase; Phase IV trials are more safe than the other Phase trials because Phase IV trials cover a wide-ranging research period after the product is licensed/permitted. At the same time cardiovascular dieases burden and costs have increased in recent years; so increase the cardiovascular Phase IV trials in Turkey can be effective to reduce the cardiovascular diseases/costs burden.

The current situation in Turkey; clinical trials was carried out with individual efforts of university hospitals and the private sector[18].

[17] The number of Phase I Clinical Research Centers in Turkey is four and the name of the centers were (Tüba, 2017): • Ege University Drug Development and Pharmacokinetic Research and Application Center (ARGEFAR), İzmir • Ege University School of Medicine, Child Hematology Clinic, İzmir • Erciyes University Hakan Çetinsaya Good Clinical Practice and Research Center, Kayseri • Istanbul Mehmet Akif Ersoy Cardiovascular Surgery Training and Research Hospital (İMAEH) Phase I Clinical Research Center, İstanbul.

[18] In total, good clinical research practice areas exist in Turkey is 5 as follows;

Clinical trials in hospitals affiliated to the Ministry of Health are carried out with individual efforts in cooperation with the university. 65 of 879 hospitals affiliated to Ministry of Health in Turkey serve as training and research hospitals under the name of A1 hospitals. These hospitals serve like university hospitals. Number of Cardiovascular Surgery Hospitals are four with 599 beds in Turkey. But there is no professional approach or institutionalization for the management of clinical trials in these hospitals (except Istanbul Mehmet Akif Ersoy Thoracic and Vascular Surgery Training and Research Hospital). Clinical trials are seriously audited studies and must meet certain standards in the areas of application. In the clinical trials conducted with the support of the public and private industry in the world but there is insufficient infrastructure in Turkey[19].

While death rates due to circulatory system decrease; the use of cardiovascular drugs (tablet usage per person, box drug use, expenditure amount) has increased (see Table 1,2,3,5). It can be interpreted that cardiovascular drugs are effective in the prevention and treatment of circulatory system diseases/deaths.

• Kocaeli University Medical Faculty Clinical Research Unit • Ankara University Medical Faculty Hematology Discipline Clinical Research Unit • Ege University PROKOM • Istanbul University Clinical Research and Excellence Center • Istanbul Mehmet Akif Ersoy Thoracic, Cardiac and Vascular Training and Research Hospital Clinical Research Center (include Phase I Clinical Research Center)

[19]For improving and development health research and development field in Turkey the plans/programs are as follows:
• Ministry of Health 2010-2014 Strategic Plan • National Science, Technology and Innovation Strategy (NSTIS) 2011-2016 • 10th Development Plan Structural Transformation Program Action Plan in Healthcare Industries • National Science and Technology Policies 2003-2023 Strategy Document • Turkey Pharmaceutical Sector Strategy and Action Plan • Ministry of Health Strategic Action Plan 2014-2017 • Presidential 100 Day Program, Ankara

Increasing clinical research in the field of cardiovascular diseases, which has a high cause of death in terms of noncomunicable mortality rates in the World and also Turkey, is important both in improving the quality of life, reducing health expenditures and increasing income. In the long term, increasing the quantity and quality of clinical researches in Turkey in the fields of cardiovascular diseases and clinical researches will directly reduce mortality rates and favourably affect economic status of Turkey as well.

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CHAPTER 5

THE RELATIONSHIP BETWEEN WOMEN'S GENDER ROLE STRESS AND THEIR ATTITUDES TOWARDS THE CONCEPT OF WOMEN'S HONOR IN FEMALE UNIVERSITY STUDENTS

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INTRODUCTION

Gender is about the status of the individuals in society, their respective roles, their duties and responsibilities, their position, how the society sees and perceives them, and their expectations (Sancar, Acuner, Üstün, & Bora, 2006). Gender, contrary to biological sex, is a concept that is not innate, is shaped within the society, and changes over time. The participation, status, and acceptance of both men and women in a society are shaped by this concept. Gender roles, on the other hand, are defined as expectations that shape the behavior of men and women regardless of biological sex (Dökmen, 2010). The roles expected from women and men are considered to be passed down by word of mouth from society to society and from generation to generation. Individuals' acceptance into society increases if the unwritten, gender-assigned roles are respected, and when behaviors in line with the expected gender role are not shown, individuals are forced to comply with the expected behavior through sanctions and reprimands (Kılıç & Kavas, 2018). The pressure of gender roles, which exist for both men and women, and expectations about how the woman should behave vary from society to society. It may even differ within a society. Similarly, the rigidity or flexibility of social expectations vary. However, the expectations that exist in a society, whether strict or flexible, limit the life of the woman, and this limitation can start from the moment the woman is born. These expectations and limitations form the basis of the concept of "gender role stress".

Gender role stress can be defined as the stress experienced by the individual regarding the gender roles expected by the society (Sabrina, Ratnawati, & Setyowati, 2016; Anyan & Hjemdal, 2018). When we look at the relationship between gender roles and stress, we can see that some events affect women more than men, because the roles and expectations assigned to women and men in society are very different (Kessler, McLeod, & Wethington, 1985). Similarly, the way women and men fight with stressors is different (Mayor, 2015). In previous studies, gender role stress for women has been associated with depression (Sabrina, Ratnawati, & Setyowati, 2016; Berry, 2017; Anyan & Hjemdal, 2018), anxiety (Aparicio-García, Fernández-Castilla, Giménez-Páez, Piris-Cava, & Fernández-Quijano, 2018), eating disorders (Bekker & Boselie, 2002; Mussap, 2007), and susceptibility to mental health disorders such as anxiety, insomnia, and social adjustment disorders (Keum et al., 2018; Anyan & Hjemdal 2018). In addition, experiencing gender role stress by women has been associated with shame (Erden & Akbağ, 2015) and somatic symptoms and sexual dysfunction (Juster et al., 2016; Kuehner, 2017; Torres-Harding, Torres, & Yeo, 2019). Gender stress in women occurs most often due to the tendency to be ashamed and excluded. It was found that the problems experienced by women (in expressing their feelings and physical constraints, in their work and sexuality) and the gender role stress are associated with the feeling of shame (Erden & Akbağ, 2015).

One of the concepts expected to be related to the female gender role stress is the concept of women's honor (Bayar, Avcı, & Koç, 2017). The concept of honor is one of the reasons underlying gender role inequalities (Tahincioğlu, 2010). The World Economic Forum's 2020 Global Gender Gap Index ranks Turkey 130th out of 153 countries (WEF, 2020). These results indicate that honor emerges as an important concept in Turkey. The concept of women's honor in Turkey is associated with humble clothing, well-behavior, obedience, and sexual purity (virginity) (Kardam, Albar, Yüksel & Ergun, 2006; Sır, 2006). In other words, honor is shaped through the female body (Turkish Parliament, Research Commission Report, 2005). The cause of 29% of the murders of women in Turkey is shown as "honor" (Turkish Parliament, Research Commission Report, 2005). Honor cultures require women to be obedient, strictly abiding by gender rules, and careful in their behaviors (Sakallı-Uğurlu & Akbaş, 2013). In other words, it may be crucial for women to control their behavior and behave in line with the expectations of the society, because the woman is associated with honor/dishonor and the possibility of being punished as a result. Therefore, it is thought that this understanding will place more pressure on women in the context of gender roles and increase their stress. Our literature review shows that expectations about gender roles may cause stress in individuals and studies are needed to enlighten this issue. There exist not many studies dealing with gender role stress in association with various variables. In Turkey, there are a very limited number of studies directly related to this concept. Accordingly, in this study, it was aimed to determine the

relationship with the attitude towards the sense of women's honor and women's gender role stress in female university students.

1. MATERIALS AND METHODS

1.1. Study Design

This is a correlational descriptive study.

1.2. Study Setting

The research was carried out at the Faculty of Health Sciences of a university in the city center of Konya. There are 5 departments (Midwifery, Nutrition and Dietetics, Social Work, Health Management, Child Development) in the Faculty of Health Sciences. The research group consisted of female students studying in these departments at the faculty during the time of the research.

1.3. Study Population, Sample Size, and Sampling Strategy

Female students studying at the Faculty of Health Sciences between March 1 and May 1, 2020 constituted the universe of the research. The sample size of the study was calculated as 500 students based on the Scale for Attitudes on Approaches to Women's Honor (SAAWH) in Vural & Körpe (2018) study, using the G*power 3.1.3 program with an average score of 82.43±6.42, within 1-point deviation, 5% error margin, and %95 power.

The students were selected by means of stratified random sampling, which is one of the probability sampling methods. In addition, a total of 100 female students from each department was planned to be accessed to ensure homogeneity, and it was aimed to reach 25 female students from each class (grades 1, 2, 3, and 4). The inclusion criteria were female students studying at the Faculty of Health Sciences and volunteering to participate in the study. Exclusion and dismissal criteria were: male students, those whose language is not sufficient in communicating in Turkish, and those who do not want to participate in the study.

1.4. Data Collection

The data were collected form female students studying at the Faculty of Health Sciences between March 1 and May 1, 2020 by the researchers using the questionnaire form. Before the data were collected, the students were informed about the purpose of the study. In an informative session, the students were explained on the following topics: volunteering is essential for participation in the study; sincere answers will contribute to the research; their answers will be kept confidential and will only be considered as scientific data; and, in order to keep the identity information confidential, names should not be written on the forms. In addition, the data were collected in their free times.

1.5. Data Collection Tool

The data collection tool in the research has 3 parts. In the first part, there is an Information Form inquiring about socio-demographic variables. The second part is the Scale for Attitudes on Approaches to Women's Honor (SAAWH) and the third part is the Feminine Gender Role Stress Scale (FGRSS).

1.5.1. Information Form

This form was prepared by the researchers and consists of 23 items inquiring about socio-demographic characteristics, such as age, school grade level, department, family type, region which the students originally come from, and the education level of the parents and profession. The form also inquires about their family structures and their views on gender roles (Güneri & Şen, 2018; Bayar et al., 2017; Koç, Avcı & Bayar, 2017).

1.5.2. The Scale for Attitudes on Approaches to Women's Honor (SAAWH)

The scale, developed by Gürsoy & Aslan in 2011, consists of twenty-five 5-point Likert type items. In the validity and reliability study of the scale, the Cronbach α coefficient was found to be 0.93 (Gürsoy & Aslan, 2011). The scale consists of 3 sub-dimensions: (1) traditional sense of honor (9 items), (2) egalitarian approach (11 items), (3) pre-marital sexuality/perception of honor (5 items). The maximum score

that can be obtained from the scale is 125, and the minimum score is 25. As the score increases, participants' perceptions of honor and attitudes towards women increase positively. A score range of 25-50 points for the overall scale indicates a traditional/gender discriminatory attitude towards women's honor. Those who score 51-75 are considered to have an undecided attitude. Those who score 76-125 are considered to have an egalitarian attitude. In the data set obtained in this study, the Cronbach alpha internal consistency coefficient was found to be 0.90, and it was calculated as 0.87 for traditional sense of honor dimension, 0.81 for egalitarian approach, and 0.78 for pre-marital sexuality/perception of honor dimension.

1.5.3. The Feminine Gender Role Stress Scale (FGRSS)

The scale was developed by Koç et al. in 2017 to measure the stress of the female gender role. The scale consists of twenty 5-point Likert type items (1: It is not stressful for me, 2: It is a little stressful for me, 3: I am indecisive, 4: It is stressful for me, 5: It is very stressful for me). The factors are not dimensional, so the total score is used in the calculation of the scale. The FGRSS score ranges from 20 to 100. Higher scores indicate higher gender role stress. The Cronbach α coefficient of the scale was found to be 0.93. In this study, it was calculated as 0.95.

1.6. Ethical Approval

Before the research, research ethics committee approval was obtained from the Faculty of Health Sciences of Selcuk University (Ethics permit no: 312/2020). Institutional permission was obtained from Selçuk University, Faculty of Health Sciences (date#13.03.2020, #28182). The primary purpose of the research was explained to all participants. Furthermore, all information related to the participants was kept strictly confidential.

1.7. Data Analysis

A statistical package program of SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze the data obtained from the study. Since the Skewness and Kurtosis values of all scales were between -1.50 and +1.50, independent samples *t* tests, one of the parametric tests, were performed (Tabachnick & Fidell, 2013). Numbers, percentage, means, and standard deviation (SD) were used as descriptive statistical values. Mean differences were calculated by one-way analysis of variance (ANOVA) and the significance test of the difference between the two means (independent sample t-test). When the group number was more than two, post hoc tests were performed to find out which group the difference originated from. The relationship between two continuous variables was assessed by the Pearson correlation analysis. Risk factors for FGRSS were determined using enter multiple regression analysis. Values $p < 0.05$ were considered significant. Multiple regression analysis was performed to

evaluate the independent associations existing between the potential risk factors and FGRSS. Independent variables that were significant at the $p < 0.05$ level in bivariate analysis were included multivariate analysis to control for confounding in regression models. Since there was a high correlation between the SAAWH total score and all its sub-dimensions ($r = 0.850$ and above, $p < 0.000$, *VIF* = 3000 and above), it was excluded from the regression model due to the autocorrelation problem (multiple linearity problem) (Alpar, 2018).

2. RESULTS

The average age of the female students participating in the study was 20.9 years (*SD* 1.9, range = 18–33) and 98.2% ($n = 491$) of them were single. Sociodemographic characteristics of the students are given in Table 1. It was found that the students who grew up in the Eastern Anatolia region, where an oppressive/coercive family structure pertains, had high FGRSS scores and experienced gender role stress ($p < 0.05$) (Table 1). Studying in different departments in the Faculty of Health Sciences, marital status, place of geographic region which they are originally from, family type, father's and mother's educational status, father's and mother's occupation, social security status, family monthly income, the item regarding “the effect of their gender on social life”, the item: “Are females and males equal?”, the family decision status, and the parents' marriage style showed no statistically significant difference with the FGRSS score ($p > 0.05$, Table 1). It was determined that students had an average of 74.3 in FGRSS (*SD* 19.8) and 99.6 in SAAWH (*SD* 15.5).

Table 1. Comparison of the Socio-Demographic Characteristics of The Students With the Average Feminine Gender Role Stress Scale (FGRSS) Score

Characteristics	***n* (%)**	**FGRSS**		
		Mean (*SD*)	***t* /*F***	***p value***
Departments of the Faculty of Health Science				
Health Management	100 (20)	75.9 (21)	*F*= 1.225	0.299
Social Services	100 (20)	76.2 (19.7)		
Midwifery	100 (20)	75.7 (18.5)		
Child Development	100 (20)	72.4 (21)		
Nutrition and Dietetics	100 (20)	71.5 (18.7)		
Marriage Status				
Married	9 (1.8)	81.7 (18.7)	*t*= -1.196	0.265
Single	491 (98.2)	74.2 (19.8)		
Type of Residence				
Village/Town/District	202 (40.4)	75.5 (19.3)	*t*= 1.118	0.264
City Center	298 (59.6)	73.5(20.2)		
Geographical Region which they are originally from				
Aegean	50 (10)	77.4 (17)	*F*= 2.471	**0.023**
Mediterranean	84 (16.8)	78.2 (19.2)		
Black Sea	25 (5)	73.2 (19.7)		
East Anatolia	21 (4.2)	82.6 (19.6)*		

Southeast Anatolia	29 (5.8)	70.9 (16.7)		
Marmara	36 (7.2)	67 (19.8)		
Central Anatolia	255 (51)	74.3 (19.8)		
Family Type				
Nucleus	437 (87.4)	74.5 (20)	*t*= 0.585	0.560
Extended	63 (12.6)	73 (18.6)		
Father's Education Status				
Illiterate/Primary School	273 (54.6)	73.6 (19.6)	*F*= 0.378	0.686
High school	131 (26.2)	74.9 (19.6)		
University	96 (19.2)	75.5 (20.8)		
Mother's Education Status				
Illiterate/Primary School	376 (75.2)	74.3 (19.8)	*F*= 0.013	0.987
High school	98 (19.6)	74.6 (20.5)		
University	26 (5.2)	74 (19.1)		
Father's occupation				
Civil servant	86 (17.2)	73.2 (20.9)	*F*= 0.836	0.474
Laborer	158 (31.6)	75.7 (20.2)		
Self-employed	138 (27.6)	72.5 (19.5)		
Retired	118 (23.6)	75.4 (18.9)		

Mother's occupation				
Employed	73 (14.6)	73 (23.4)	*t*= -0.545	0.587
Not-employed	427 (85.4)	74.6 (19.2)		
Social security status				
Yes	428 (85.6)	73.9 (19.3)	*t*= -1.085	0.281
No	72 (14.4.)	77 (22.5)		
Monthly income				
Less than 891 TL	8 (1.6)	73.8 (16.9)	*F*= 0.064	0.979
891-1500 TL	48 (9.6)	75.4 (19.3)		
1501-2500 TL	131 (26.2)	74.5 (18.7)		
Over 2500 TL	313 (62.6)	74.1 (20.5)		
The status of the effect of gender on social life				
Yes	471 (94.2)	74.5 (19.7)	*t*= 0.816	0.421
No	29 (5.8)	71.2 (21.4)		
Are male and female equal in terms of gender?				
Yes	310 (62)	75.1 (20.2)	*t*= 1.056	0.292
No	190 (38)	73.1 (19.1)		
In-family decision-making process				
My father makes the decisions	205 (41)	73.3 (19.9)	*F*= 2.692	0.069
My mother makes the decisions	69 (13.8)	79.4 (17.5)		

Mother-Father-Children make decisions all together	226 (45.2)	73.7 (20.3)		
Family status				
Oppressive/challenging	47 (9.4)	79.7 (18.5)*	*t*= 3.976	**0.019**
Democratic	230 (46)	75.6 (19.7)		
Just	223 (44.6)	71.9 (20)		
Parent's marriage type				
Arranged	370 (74)	73.5 (20.1)	*t*= -1.556	0.121
Love marriage	130 (26)	76.6 (18.9)		

t= Independent sample t test, SD=Standard Deviation

*F=One-way analysis of variance (one-way ANOVA, *post-hoc test*

A positive and weak relationship was found between the FGRSS stress scores and SAAWH total score and sub-dimensions ($p < 0.001$, Table 2).

Table 2. Bivariate Correlations (Pearson's R) Analysis Between the Feminine Gender Role Stress Scale (FGRSS) and the Scale for Attitudes on Approaches to Women's Honor (SAAWH) and its Sub-Dimensions

Parameters	**Feminine Gender Role Stress Scale (FGRSS)**	
	r	***p***
The Scale for Attitudes on Approaches to Women's Honor (SAAWH)	0.439	< 0.001
Traditional Concept of Honor	0.377	< 0.001
Egalitarian Approach	0.375	< 0.001
Sexuality/perception of honor before marriage	0.320	< 0.001

r = Pearson correlation coefficient

Variables that were significantly associated with the total score of the FGRSS were entered into a Stepwise multiple regression analysis to further investigate these associations. The variables that were found meaningful as a result of the statistical analysis, namely, traditional sense of honor, egalitarian approach, pre-marital sexuality/perception of honor, geographical region which they originally come from (Eastern Anatolia), family structure (oppressive/coercive), were included in the multiple regression analysis. The geographical region they originally come from (Eastern Anatolia) and the family structure (oppressive/ coercive) variables were eliminated as a result of the analysis. The mean score of the FGRSS was analyzed as a continuous variable and the other variables were used as dummy variables. The regression model for the FGRSS was significant (F= 24.529, p < 0.001), and accounted for 19% of the variance. Traditional sense of honor (a sub-dimension of SAAWH) (t=4.281, p < 0.001), egalitarian approach (a sub-dimension of SAAWH) (t= 3.810, p = 0.003), premarital sexuality/perception of honor (a sub-dimension of SAAWH) (t= 2.504, p < 0.001) were uniquely associated with the FGRSS.

Table 3. Multiple Regression Analysis Results Related to Students' Variables that are Significant with the FGRSS

FGRSS	***B***	**Std. Error**	**Std. *β***	**% 95 *Cl***		***t***	***p***
				Min	**Max**		
Constant	17.349	5.827	-	5.900	28.798	2.977	**0.003**
Tradition concept of honor	0.590	0.138	0.214	0.319	0.861	4.281	**0.000**
Egalitarian approach	0.572	0.150	0.194	0.277	0.867	3.810	**0.000**
Pre-marital sexuality/perception of honor	0.495	0.198	0.122	0.107	0.883	2.504	**0.013**
Geographical region (East Anatolia)	3.017	4.144	0.030	-5.124	11.158	0.728	0.467
Family type (Suppressive/coercive)	4.578	2.783	0.067	-0.891	10.047	1.645	0.101
***R*= 0.446**	***R*²= 0.199**			***Adjusted R*²= 0.191**			

3. DISCUSSION

This research reveals that traditional sense of honor, egalitarian approach, and pre-marital sexuality/perception of honor affect the risk of women's developing gender role stress by 19%. However, it was determined that female students originally come from the Eastern Anatolian region with a "suppressive/coercive" family structure experience the gender role stress more.

According to the multivariate regression analysis results, students with a traditional sense of honor have a higher gender role stress. Similar to our research results, in a study conducted in 8 universities in Ankara, it was stated that the number of students who displayed a positive

attitude towards traditional honor was higher than expected (Gürsoy & Özkan, 2014). In addition, in another study, it was emphasized that honor is used in the sense of sexual activity outside marriage, and it is emphasized that when it comes to honor, the prohibition of extramarital sexual intercourse and the protection of virginity are considered as the basis of honor for people of all ages, classes, and genders (Bora & Üstün, 2008). However, in study involving 446 women studying in different universities in Turkey, it was reported that the variable of "traditional definition of honor" may not contribute to the prediction of gender role stress (Bayar et al., 2017). While it is not a problem for a man to experience sexuality/sexual relations without getting married in a specific culture, even this phenomenon is enforced by the "real men do it this way" or "it a piece of cake for men" approach; however, if a "girl"/woman has sexual intercourse without marriage, she would not be treated well in the society (Dinçer, 2007). Even the behaviors of the woman, her style of clothing, her talking a lot, her opposition to the man, her requesting a song from the radio for her boyfriend, and her walking around can be associated with her honor. The upbringing of the young people according to the traditional moral structure of the society since the childhood and the values learned in childhood may be more effective in their future lives. For this reason, it is inevitable for university students to reflect their thoughts and values they have acquired since childhood. In addition, the change of thoughts and attitudes of young people who were raised in a society where social expectations and cultural conditions predominate often does not occur.

Our results showed that having an egalitarian approach has been found to be a risk factor for gender role stress. In studies conducted with university students, it has been reported that students with an egalitarian approach have high gender role stress levels (Gürsoy & Özkan, 2014; Bayar et al., 2017). Egalitarian gender roles can put pressure on individuals, just like traditional gender roles. According to the United Nations Human Rights Council (2014), stereotypes regarding gender role can be both positive and negative. In other words, expressions that seem positive may have a gender role stereotype (UNHCR, 2014). Therefore, it can be a source of stress. In addition, women may need to make extra efforts to achieve this equality, because according to the report published by the World Economic Forum's 2016 gender equality, Turkey lagged behind many countries and ranked 130th out of 144 countries (WEF, 2016).

As a result of the regression analysis, the gender role stress of students with a pre-marital sexuality/perception of honor is higher. In this scale, there are items such as “Virginity is the symbol of honor in women”, “The virginity of women reinforces the trust of men in women”. In Turkish culture, the honor and virginity of women symbolize the men’s and the family’s honor. The basis of this understanding is the gender discrimination produced by the patriarchal structure (Gürsoy & Özkan, 2014). The society that offers men comfort in many areas expects the woman to act in accordance with the customs in the society she lives in and expects her to lead a life under the supervision of the man using the “honor culture”. This

discrimination manifests itself most prominently in the control of the woman's body (Bora & Üstün, 2008). Gökalp (2003) emphasizes that the limited freedom of women's decision-making about her own body and future in the traditional woman-man relationship is stressful for the woman. Bayar et al. (2017) stated that the most significant predictor of female gender role stress is pre-marital sexuality/the concept of honor. In another similar study where students' submissive behaviors and the gender roles expected from them were discussed, the main topics that the participants thought families expected most from them were: "Being at home/dormitory early in the evening", "Not going out without permission", "Not having sexual intercourse before marriage" and "respecting the adults". Here, too, it is observed that students are aware of the expectation about virginity. When the literature is examined, there exist research findings emphasizing that the concept of pre-marital sexuality is important in explaining the stress that women experience in line with their gender roles (Koç et al., 2017). In a dissertation, it was revealed that 42.5% of 200 university students think that women should remain virgin until they get married (Okyay, 2007). Therefore, the concept of honor in Turkish culture is bound to be a concept that affect significantly the gender role stress of women.

The data of this study were obtained from women from many cities, cultures, and socioeconomic levels. On the other hand, the study is limited by the facts that the participants were all from a single faculty of a university and no male students were included in the study.

Considering that gender role attitudes are shaped at an early age, it is thought that it may be beneficial to carry out similar studies with different age groups. Efforts to subdue the rigid perspectives brought about by women's gender role stress risk factors (traditional honor concept, egalitarian approach, pre-marital sexuality/perception of honor) will provide an important improvement in reducing women's stress.

4. CONCLUSION

The traditional sense of honor, egalitarian approach, pre-marital sexuality/honor perception affect the risk of women's experiencing gender role stress at the rate of 19% ($F = 24.529$, $p < 0.001$). However, due to the geographical region (Eastern Anatolia) which the female students originally come from and the family structure (suppressive/coercive family type), they are more likely to experience gender role stress, but it was not found as a risk factor.

University students' gender role stress is affected by the traditional sense of honor, egalitarian approach, and pre-marital sexuality/honor perception. In addition, the findings revealed that the "honor culture" of the family and the society, rather than the university education, played a critical role in the formation of the gender role stress of the students. Accordingly, it may be recommended to organize informative conferences, seminars, or workshops that will contribute to gender equality for university students.

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CHAPTER 5

HEALTH CARE IN THE TERMINAL STAGE

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INTRODUCTION

The terminal stage called the last stage of life is regarded as the stage in which death is expected within weeks or months. At this stage, social and psychological support provided by experts is needed for patients and their families. Hospice care, which is care provided to patients in the terminal term, focuses on comforting the last days of patients and improving the life quality of them (Peykerli, 2003). The terminal stage is called the last before death and defined as a period in which all the treatment processes applied to a patient. This process is generally completed. Positive results are not obtained from the treatment. Death is unavoidable at the end of the treatment process. All kinds of remedies are tried.

The terminal stage, which is called the last period of life, is a phase in which not only the elderly people but also all the people with a disease without treatment and waiting for death (Civaner, 2003). With the increase in the number of chronic diseases and the aging of the population regularly, it has emerged that the need for health care services provided to patients within the terminal term has gained a very different direction. To query and advance the quality of health care services that are delivered, it has become necessary to make breakthroughs. To ensure healthier the last times of patients in the terminal period, health facilities should be managed both in terms of managerial (adequate human resources, professional care team, adequate equipment, etc.) as well as overcoming the legal and judicial barriers to the legislation, and political steps are needed to eliminate

any administrative, financial, legal and legal barriers to the furthest deterioration of patients and their families.

For end-of-life patients, priority should be provided for increasing the quality of life rather than delaying death and keeping it as constant as possible (Karan, 2006). Despite advances and signs of progress in medicine and technology, the rise in the number of untreatable diseases such as cancer, AIDS cannot be prevented. In all these processes, it is quite significant to advance the quality of life of patients and their relatives and to provide services that will enable them to live a humane life from disease to the death process (Cayak & Ateş, 2011).

In the process of reaching death in peace and dignity of terminal stage patients, the patient's choice of the death place and the relatives of the patients is important to better the quality of life at the time of death, even the quality of death. In this chapter, it is also mentioned what the death place preferences of patients in the terminal stage maybe and some factors that affect these preferences. In many countries, treatments provided for end-of-life stage patients that separated from classical intensive care and hospital services have been transferred to private care centers.

1. TERMINAL STAGE AND TERMINAL HEALTHCARE

During the last 20 years, there have been significant developments in health and especially in medicine, but despite these developments and advances, the prevalence of many fatal and incurable diseases

continues, increasingly (Peykerli, 2003; Schonwetter, 1996). Medicine that develops and progresses, which tries to find a treatment for deadly diseases, regards death as an enemy to itself (Civaner, 2003). The psychological, spiritual, physiological, and social status of an individual suffering from a fatal disease has a devastating effect both on his family, relatives, and people with the material and spiritual tie. This situation creates some problems in both patient and family and the healthcare team involved in the treatment process.

The patient in the terminal term refers to who lives in the last days and dying patient. Patients of the terminal term may have fears such as burdening others, loss of physical, and mental abilities while dying, expecting pain related to death and dying prematurely before achieving important life goals (Birol, 2004). Health care in the terminal period is also explained as the management of the last days, weeks, and months, originating from the point where the decline in the patient's state of health is quite evident (Yennurajalingam & Bruera, 2011).

All activities aimed at meeting the needs of patients and maintaining a better life of them in the terminal stage are called end-of-life care (MEB, 2015). The care and death of patients nearing death are one of the most difficult aspects of healthcare professions. There are three important situations (pain, loneliness, and isolation) faced by patients in the terminal period. Fatal diseases cause different psychological responses in each patient (Peykerli, 2003). Fatal diseases cause different psychological responses in each patient.

1.1. Nursing Care in the Terminal Stage

It is important how much nursing care is required in the terminal period and also the number of nurses should be sufficient in providing nursing services (Nakanishi et al., 2017; Komaromy, 2008; Sherman et al., 2015). The main purpose in the care of patients who will die should be to ensure the physical and spiritual comfort of the patient and increase the quality of the remaining lifetime (Peykerli, 2003). The importance of nursing, the role of nursing skill, and the feelings and thoughts of nurses about death help to conduct the progression of the treatment positively (Peters et al., 2013). In this context, nurses play the most critical role in the service provided to patients and relatives in the terminal term. Nurses address the problems of terminal patients, help them deal with their problems effectively, and to create supportive resources.

Nurses who serve the patient in the terminal term have significant responsibilities. These responsibilities include the fears of the patients, protecting the individuality and family integrity of the patient, planning for emotional and physical empowerment of the family and preparing the family for the mourning process, controlling the symptoms, and ensuring the patient's peaceful death. During the care of the patient going through the last days of life, the nurses must have the knowledge, skills, and understanding to meet the emotional and physical needs of the patient. At the same time, nurses must understand and accept the patient's feelings, to provide effective psychosocial support to the patient and the family (Bahar, 2007).

1.2. Terminal Term Patients and Experiences of Their Relatives

One of the most needed issues in this term is not only the physical and emotional support to be given to the patient but also the spiritual support they need to the patient's family and relatives. In this process, both relatives and all members of the treatment team carry jointly out all stages of the care process (Bahar, 2007). Therefore, there is a mutual interaction between the patient, patient relatives, and the care team members in all the processes from the beginning of the care to the completion.

Reactions related to death, deprivation caused by death according to the level of emotional and cognitive development of individuals, and the socio-cultural characteristics are experienced in four stages (Wheeler, 1996).

Shock and Numbness Period: In a sudden and unexpected time, with the sadness of one person's death who is loved, it is a difficult situation for the relatives of the patient that he/she is to be no longer among the lovers (Grey, 2010). This process, which lasts approximately two weeks after the death of the patient, is seen as the period in which the relatives of the patient are shocked and over-emotional. They often experience an explosion of emotions and behavior that usually takes 15 minutes, such as sobbing and crying by hitting the chest, screaming, and punching the walls. Such emotional and behavioral situations are difficult to overcome (Wheeler, 1996).

Researching and Longing Period: This period covers two weeks to four months after the loss. The person who experiences separation anxiety misses the deceased relative and displays thoughts and emotions as if s/he were alive even though s/he knew that the relative was dead. This event is an obstacle for the individual to accept the truth. The person who experiences the loss feels lonely, and it is difficult to return to daily routines such as sleeping, eating, drinking, and social activities for a while (Wheeler, 1996). Individuals who experience or are likely to experience separation pain are likely to struggle a separation anxiety disorder over time. In this period, which is an emotionally painful process, the person expects the relatives as if he will come back (Grey, 2010). On the other hand, nurses who are in close contact with the terminal period patients and provide care cause anxiety about death due to their experiences (Peters et al., 2013).

Period of Disorder and Clutter (Disorganization): This term is like clinical depression which appears between 5 and 9 months after the death of a person loved. The individual experiences feelings of depression and inadequacy. S/he does not feel physically and emotionally well. S/he may be difficult to accept social support. The individual accepts the changes caused by the loss and to reorganize life towards the end of this period (Wheeler, 1996). One has solved many of the grief and mourning stages. By expressing his lost feelings, the person accepts that what happened cannot be returned. At the same time, the person often performs his routines. It is now possible to talk about the changes that have happened to a certain extent after the person who died. And now it is a sign that a period of

sadness has passed. At the end of this period, the person is even more ready for a new loss (Grey, 2010).

Rearrangement Period: Approximately one year after losing a relative, the feeling of grief diminishes and tends to be more functional with the increase in self-esteem and trust (Wheeler, 1996).

1.2.1. Ways Helping For Sad Family Members

In the terminal stage in which the stress levels of family members of sick people are intense (Elçigil, 2006), for an appropriate death of the patient and relatives; they want that implementation of an efficient pain and symptom treatment, making clear decisions about the process and implementation of these decisions, not applying of useless and exhausting medications that prolong the death process, being able to ready to die and to say goodbye to patients' relatives, reviewing the life, the ability to spend time with relatives, respect for personality integrity, and being able to contribute to other people (gifts, time, or information sharing) (Thompson & McClement, 2006). For these reasons, the role and responsibility of physicians are extremely important for the decisions of patients and their relatives. Because the physicians have to make dozens of decisions about the future of patients every day. While making these decisions, the decisions should be both sound and offer correct management about diagnosis and treatment (Hui & Bruera, 2014).

In a study conducted by Babaoğlu & Öz (2003), it was obtained that the emotional and social problems of the spouses who care for cancer patients in the terminal period affect each other mutually.

1.3. Death Place Preferences Of Patients in the Terminal Stage

When patients are confronted with the fact that they are close to death or that their living time is limited, their discomfort evolves into even more pronounced. They worry about the last days of life and consider whether they will be a burden for others. During this stage, patients' spiritual and religious tendencies increase, they seek solutions to conflicts, and they begin to question the meaning of life or death.

Within the terminal stage, when the preferences of the death place of cancer patients are examined, it is seen that they prefer to die at home, hospital, or hospice. For example, 17% of deaths occurred at home in the United States in 1994. Most people who die at home are usually cancer or AIDS patients. Some studies report that these patients are younger, while other studies report that over 65 years of age have lost their lives at home. Those who die at home belong to a higher social class and/or have more economic resources. They and their families thoroughly accepted the fact that they would soon die. They have a caregiver, do not live alone, and their relatives who are primarily interested in them are healthy. The patient's self-care can be met at home (Işıkhan, 2008).

In Turkey, there are few studies about the preferences of the death place of cancer patients. According to the results of a national study conducted on 200 adults regarding their preference for a hospice or a hospital death, 47% of them prefer to die with home caregivers. Besides, 54% prefer to die in hospitals where they think they can get

better care. Over 60% of deaths in urban areas are in hospitals (Işıkhan, 2008).

1.4. Home Care in the Terminal Stage

Home care service, which is part of health services, is the delivery of necessary health services to patients and their families who are under medical control in the environment in which they live and where they live. Home care aims to minimize the effects of the disease and insufficiency by achieving maximum treatment by minimally affecting daily living conditions, while at the same time increasing life increases (Karamercan, 2001). In a study conducted on medical staff in Spain, they think more appropriate in which terminally ill should be given medical care at home (Osuna et al. 1998). Palliative home care services have been established in some countries around the world (Romania, Croatia, Bosnia and Herzegovina, Bulgaria, Albania, etc.). Home care services for end-stage patients in countries such as the USA, Germany, and England are provided in hospice and palliative care centers (Milicevic, 2002).

1.5. Patient Rights in the Terminal Stage

In the end-of-life stage, each patient may determine the treatment options, as well as the right to determine where to end his life. In the last stages of life, individuals should be given the choice of where they want to live their death. Among the factors that may affect the death place preferences of cancer patients in the terminal stage include the patient's social environment and plan of the lifetime, the knowledge and experience of the caregivers of the patient, the concern

related with peace and well-being of the patient's self-caregiver / family, the caregivers' attitudes and volunteering for care, symptom management, fear of losing the respectability of the patient, and the patient's experiences with hospitals can be counted. Some rights in the terminal stage are as follows (Çavdar, 2011):

- The right to know that the disease is serious and that the patient may die,
- The right to receive treatment/care until death,
- The right to die in a hopeful environment where one is peaceful, respected and surrounded by people he loves (not surrounded by tubes and machines),
- The privacy right,
- The right to take part in decisions related to care,
- The right not to die alone,
- The right to be answered honestly,
- The right to die in dignity and peace,
- The right to be cared for by people who are sensitive, knowledgeable and try to understand their loved ones,
- The right to die free of pain and other disturbing problems,
- The right to not be deceived and not to lie,
- The right to expect respect for his body after death.

1.6. Ethics in the Terminal Stage

The concept of ethics, which is different from the concept of morality, is a concept that tries to reveal whether a person's action is right or wrong, and it is also a branch of philosophy. This concept appears in

almost every field (Fischer, 2004). However, this concept has distinct importance within the health sector. Treatment methods and plans applied to patients in the last period of life, healthcare services, and plans suggest the concept of ethics for practitioners. Human requirements continue from birth to death and even after death. Ethics in the terminal term is intertwined with the concept of medical ethics.

Ethical decision-making is one of the issues that leave health professionals in the lurch and inadequate situation in the terminal stage and compels them to make decisions about patients and their families (Demir, 2016). Euthanasia, which is a method used to relieve the suffering of patients with a terminal illness, is not ethical according to the World Medical Association (Er, 2019). Euthanasia is demanded by patients who cannot bear the pain, those who try to prolong human life by many methods that do not have benefits and curability bring with it many ethical problems. Both the patient and the disease's needs and the requirements of medicine should be met in a common denominator. This also emphasizes the structuring of the health system (Civaner, 2003).

1.7. The Relation between the Terminal Stage and Religion

The patients in the terminal stage have experience in a series of moral and spiritual subjects such as guilt, shame, despair, loss of reputation, loneliness, anger against Allah, abandonment by Allah, out of control, grief, and spiritual anguish. And this is not limited to these experiences. In terms of the situation of illness, the spiritual status of the patients, the religion that they believe, and the religious

requirements are of great importance. In the context of freedom of belief and the necessity of patient rights, some actions should be taken to ensure that the patients who express their loyalty to the sect/community they belong to in the Islamic religion reach to the leader of the sect/community or to reach the priests for patients with Christian beliefs, and they should be helped in their last periods in peace (Breitbart & Alici, 2014). It is thought that the political and bureaucratic situation of the country is decisive in giving moral or religious support. In countries that suffer from freedom of religion and conscience, there will inevitably be serious problems in providing religious and spiritual support for terminal patients in public institutions and organizations responsible for the provision of services in a system and order where religious beliefs are ignored.

1.8. Social Rehabilitation in the Terminal Stage

Rehabilitation, is derived from the word rehabilitate, is defined as helping a person to maintain their normal life after illness or in prison, according to the definition in the Oxford Wordpower Dictionary.

According to the definition made by World Health Organization, the word rehabilitation is defined as *"a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments*."[22]

[22] https://www.who.int/disabilities/world_report/2011/chapter4.pdf, Access date: 24.10.2019

The rehabilitation services are divided into medical rehabilitation and social rehabilitation. Medical rehabilitation, known as the rehabilitation method used for correction of posture disorders, using limb prostheses, minimizing hearing and vision deficits, is a service provided to improve the quality of life and correction of physical permanent disorders and disabilities. Social rehabilitation, aimed at the active participation of people with disabilities or disabilities in daily life without being dependent on others; covers work adaptation, finding new jobs or teaching.[23] When investigated the literature, it is shown that the concept of social rehabilitation is mostly used for rehabilitation services of elderly people.

Increasing the quality of life is extremely important in rehabilitation services. Social rehabilitation services have emerged due to reasons such as increasing the quality of life of individuals in special needs groups (children, families, elderly women, criminals, disabled people who need protection).[24]

The truth of death is the head of the common significant concerns in people's lives. It is quite normal to be afraid of death, in which every person will experience only one time in their life. One of the most notable features of the terminal period is that people are experiencing the most intense feeling of a hidden life, and the fear of death is the most felt period (Bahar, 2007).

[23] Patient and Elderly Services, Rehabilitation Services, Republic of Turkey Ministry of National Education, Ankara, 2016

[24] Patient and Elderly Services, Rehabilitation Services, Republic of Turkey Ministry of National Education, Ankara, 2016

Despite the important advances in medicine and technology in recent years, there are many compelling factors in terms of providing the psychological, social, psychological, and physiological support to be given to the patient and his family since some diseases continue to be seriously fatal.

2. HOSPICE AND PALLIATIVE CARE IN THE TERMINAL STAGE

There are many similar aspects of hospice and palliative care. Both concepts try to explain the physical, spiritual, and emotional aspects of patients in the terminal stage. However, there are some differences between hospice and palliative care (Hill, 2007). In this section, the concepts of hospice and palliative care will be briefly explained.

2.1. Hospice Care

The Latin word hospice has two different meanings: guest and host (Cayak & Ateş, 2011). Hospice is the institution that provided care for patients in the terminal stage (Elçigil, 2012).

In the modern sense, hospice, which is a new concept, began to develop rapidly with the establishment of St. Christopher's Hospice in England in 1967. It was founded by Dame Cicely Saunders, known as the founder of the modern hospice movement (Graham & Clark, 2007).

Cicely Saunders, one pioneer of the Hospice movement and the founders of the first modern hospice, who was born in 1918, was educated first as a nurse, then as a social worker and ultimately in

medicine. During his tenure at the hospital, he realized the physiological and mental requirements of dying patients who felt lonely and isolated, and while following up on patients who died of cancer, she was interested in cancer treatment and especially pain control. For this reason, she started medical education and completed her education as a medical doctor in 1957. By putting forward the concept of total pain, she developed the use of strong opioids based on the principle that continuous pain requires constant control. She recommended using analgesics not only to relieve pain when there was a pain but also to prevent pain continuously and regularly. She contributed importantly to this field by combining all of her skills in the branches she specialized in (Milicevic, 2002).

2.1.1. The Principles of Hospice Care

Maintaining the quality of life at the highest level in the terminal stage and symptomatic treatment is important. During this stage, pain and symptoms should be relieved. Hospices, which prevent the onset of pain and symptoms, are the institutions where the patients in the terminal stage are cared for. These institutions admit to untreatable patients as well as patients with a fatal diagnosis. Care is taken to arrange the hospices in a manner appropriate to the home environment. Thus, patients spend their final stages painlessly and peacefully by taking the care under the conditions of the home environment (Birol, 2004).

Hospice care and principles should be as follows (Özyılkan, 1999):

- Ensuring control of disease-related symptoms of patients,

- Follow-up of patients monitored in hospice in their homes later,
- Multidisciplinary team care,
- Providing continuous service,
- To be accepted as part of the medical team of the patient and his family,
- Supporting patient's relatives at the time of death and after death,
- The use of volunteers.

A significant goal of hospice care is to keep terminal cancer patients in their homes as long as possible and to use the days spent in the hospital only when necessary.

2.2. Palliative Care in the Terminal Stage

The definition of palliative care was first made by the World Health Organization (WHO) in 1986, and major improvement was made in this field. According to the definition given by WHO (1986), palliative care is all care for patients that do not respond to treatment (Elçigil, 2006; Elçigil, 2012) and renewing in 2002, it was defined as; when the patient and his family encounter a life-threatening problem, to be identified of pain and other physical, psychosocial and spiritual problems, carefully evaluated and treated, preventing the patient from suffering and is an approach that advances the patient and the family's the quality of life (Graham & Clark, 2007; Elçigil, 2012). Palliative care, an essential part of clinical practice, is an interdisciplinary therapeutic model for the management of patients with incurable,

progressive disease (Bruera & Portenoy, 2001). Palliative care can be provided by palliative medicine specialists in hospices, as well as provided by many specialist professional groups, including primary care practitioners, oncologists, intensive care specialists, hospitalists, and other clinicians (Block, 2014).

Among the important issues in the palliative care process are the approach to the patient and his family. This process becomes functional with the effective management of pain and other painful symptoms by combining psychosocial and spiritual care, taking into account the needs, preferences, values, beliefs, and cultures of patients and their families (Yennurajalingam & Bruera, 2011).

Over time, the concept of palliative care changed and was used in the early 1990s to care for individuals dying of cancer in America. Because the vast majority of palliative care programs were initiated for cancer patients, but individuals with other chronic diseases such as heart failure and lung disease also began to see a great benefit from palliative aspects (Elçigil, 2012).

2.2.1. Characteristics of Palliative Care

Several of the features of palliative care, which are also characteristics of high-quality oncological care, are specified by the WHO (Davies & Bailey, 2006).

These features are presented in the following substances:

- Palliative care helps the patient get rid of pain and other disturbing symptoms.

- It seems that life goes on and dying is a normal process.
- There is no purpose to expedite or postpone death in palliative care.
- Palliative care deals with the psychological and spiritual aspects of patient care as a whole.
- It provides support to help patients live as actively as possible until their death.
- It provides a support system to help the patient cope with his or her illness and his family's sorrows.
- If requested, it uses a team approach to help patients and their families address and write their needs, including patient-death counseling.
- It improves the quality of life and positively affects the course of the disease.
- It is applied at the beginning of the disease, along with other treatments designed to prolong the patient's life, such as chemotherapy or radiotherapy, and includes research that is needed to better understand and manage unpleasant clinical complications (Graham & Clark, 2007; Breitbart & Alici, 2014).

CONCLUSION

The quality of the care services offered in the terminal period significantly affects patients' preparations for the death process. All members of the care team contribute to an effective improvement in the quality of care service. The role and responsibility of nurses among these members are more notable than other members of the

team. Team members have a considerable responsibility to strengthen the bond established with patients' families and others who contribute to the care. Internalizing the roles of family members or other caregivers during the care offered at the patient's home constructively affects the patient's morale and motivation. During this period, patient rights should be paid maximum attention within the framework of ethical principles, and sensitivity should be shown to their religious and spiritual values; efforts should be made as much as possible to socialize the patient. On the other hand, palliative care centers and hospices, which have an important place in the terminal period, should make investments that will prioritize the interests of the patients.

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CHAPTER 6

ATHEROTHROMBOTIC CARDIOVASCULAR DISEASES AND NEW ORAL ANTICOAGULANTS

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INTRODUCTION

The incidence of atherosclerotic illnesses increases with aging (Benjamin et al., 2017). Coronary artery disease (CAD) is the cause of death on the earth by giving rise to acute coronary syndromes (Bansilal, Castellano, & Fuster, 2015). The peripheral artery disease (PAD) can cause ischemia and amputation of the leg. Patients with PAD have a highened risk of mortality and morbidity owing to the risk of repetitive ischemic events in the leg at a rate of 10% per year (Jacomella, Corti, & Husmann, 2013). In addition, increased risk of mortality is significant in patients with PAD due to the accompanying CAD and cerebrovascular disease (CVD) risk. The cardiovascular mortality risk increases up to 11 times in patient with PAD compared to patients with non-PAD (Criqui et al., 1992). Atherothrombotic events involving carotid artery atherosclerotic disease (CAAD) constitute 3/4 of the ischemic strokes (Pastori et al., 2019). The annual stroke risk in patients with CAAD according to the degree of stenosis is between 0.3-11.1% (Langhoff, 2017). The risk of cardiovascular events increases from 8.4% to 18.1% in medically treated patients with symptomatic CAAD (Pastori et al., 2019).

Atherothrombosis is induced by atherosclerotic plaque rupture. Plaque rupture exposes a thrombogenic subendothelial matrix, and resultant endothelial damage causes tissue factor 7 (F7) and platelet activation (Hess et al., 2017; Stachon, Ahrens, Bode, Zirlik, & thrombolysis, 2016). Activated tissue factor induces factor 10 (FX) and thrombin

formation. Thrombin leads to fibrin formation and thus formation of thrombosis on the atherosclerotic plaque (Bauersachs, Zannad, & haemostasis, 2018; Chan & Weitz, 2019; Jacomella et al., 2013). Atherothrombosis is also characterized by endothelial damage with low grade inflamation that needs to be addressed (Badimon, Storey, Vilahur, & haemostasis, 2011; Borissoff, Spronk, & ten Cate, 2011; Popović et al., 2012). Factor Xa and thrombin activation have a role in inflammation as well as thrombosis (Borissoff, Spronk, Heeneman, & ten Cate, 2009; Borissoff et al., 2011; Chan & Weitz, 2019; Jacomella et al., 2013). Oral anticoagulant agents reduce endothelial damage with their antiinflammatory effects (Borissoff et al., 2011). Thus, addition of Factor Xa and direct thrombin inhibitors (NOACs) to antiplatelet therapy in this fibrin formation cascade is important to provide more effective treatment.

According to the REACH registry, 15.9% of the population had CAD, PAD and / or cerebrovascular disease and 65.9% had monovascular disease (Bhatt et al., 2006), and could not achieve optimal protection from atherothrombotic diseases with antiplatelet therapy only (Alcocer et al., 2014; Berger et al., 2011; Bonaca et al., 2015; Cacoub, Bhatt, Steg, Topol, & Creager, 2009; Tricoci et al., 2012). Despite antiplatelet therapy, ≤5-10% of patients with PAD or stable CAD experienced a recurrent ischemic event (Gutierrez et al., 2018; Suárez et al., 2010). Therefore, ways of more effective treatment were investigated by adding anticoagulant agents effective in thrombus formation. Based on this, vitamin K antagonist (VKA) was added to

aspirin in patients have atherosclerotic cardiovascular disease. Combination warfarin with aspirin (INR 2.0-3.0) in comparison to aspirin alone, reduced recurrent MI by up to 46% after a myocardial infarction (MI), ischemic stroke by 56% and revascularization by 80%, but increased major hemorrhage conditions by 2.5 times (Rothberg, Celestin, Fiore, Lawler, & Cook, 2005). In a large meta-analysis, the combination of acetylsalicylic acid (ASA) plus warfarin in ACS (acute coronary syndrome) provided significant advantage in terms of reduced major adverse events compared to ASA only, but increased risk of hemorrhage (Andreotti, Testa, Biondi-Zoccai, & Crea, 2006). In another study, compared to aspirin alone, low-doses of oral anticoagulants (INR < 2.0) combined with aspirin showed a 1.3 - fold increase in major hemorrhage, but no significant clinical advantage in terms of major advers events over aspirin alone (S. S. Anand & Yusuf, 1999). Warfarin Antiplatelet Vascular Evaluation (WAVE) trial investigated combination of antiplatelets therapy with oral anticoagulants to reduce atherothrombotic complication rates in patient PAD. In this study, compared to ASA treatment only, the combined use of warfarin in the normal range with ASA did not concequence in a significant reduction in major adverse events and, but was seen increased by 3.4 times of major hemorrhage events (S. Anand, Yusuf, & Montague, 2007; WAVEInvestigators, 2006). Thus, the use of warfarin has been limited due to high bleeding rates. In the TRA 2 P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events-Thrombolysis in Myocardial Infarction 50) trial, the use of vorapaxar (PAR-1

antagonist) reduced acute limb ischemia (ALI) and require for peripheric artery revascularization in PAD, but the possibility of major advers events did not reduce and moderate-to-severe bleeding events remained significantly high (Bonaca et al., 2016). In the OASIS-5 trial (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes), 1 mg / kg enoxaparin dose and FXa inhibitor low-dose (2.5 mg) fondaparinux were randomized to patients with ACS. In that study, low-dose fondaparinux reduced major bleeding rates by about half compared to full-dose enoxaparin, with similar efficacy (Anderson et al., 2010; Yusuf et al., 2006).

NOACs comprise dabigatran, which functions by directly inhibiting thrombin, and rivaroxaban, apixaban, edoxaban and betrixaban, which function by inhibiting factor Xa. From 2010 to June 2017, various NOACs were approved by the FDA; dabigatran and apixaban to reduce systemic embolism and stroke in patients with non-valvular atrial fibrillation; rivaroxaban and betrixaban for prophylaxis of venous thromboembolism (VTE); edoxaban to treat VTE and to reduce the risk of stroke in non-valvular atrial fibrillation were approved by the FDA in adult patients. Today, these approvals are as follows: dabigatran, rivaroxaban and apixaban are for systemic embolism and stroke in nonvalvular atrial fibrillation as well as treatment of VTE; edoxaban for nonvalvular atrial fibrillation and VTE treatment; betrixaban for VTE propylaxis. However, only low dose rivaroxaban was at recent time accepted by FDA to decrease the risk of major cardiovascular events, such as myocardial infarction, stroke and death in chronic CAD or PAD (Chaudhary et al., 2019).

Rivaroxaban shows antiplatelet and anticoagulant effects by reducing thrombin production and thus provides anti-inflammatory and endothelial protective effects, which reduces the risk of atherothrombotic complications (Bauersachs et al., 2018). The combination of rivaroxaban with antiplatelet treatment increased antithrombotic activity compared to antiplatelet treatment or rivaroxaban alone (Perzborn, Heitmeier, Laux, & therapeutics, 2015). Moreover, rivaroxaban treatment has been shown to decrease in mortality and morbidity with in patients with ACS (Mega et al., 2012). In this manuscript, we discussed the therapeutic efficacy of NOACs for prevention and treatment of atherothrombotic cardiovascular diseases with literature review.

1. PHARMACOLOGY AND SIDE EFFECTS OF ORAL ANTICOAGULANTS

Rivaroxaban (Ahrens, Lip, Peter, & haemostasis, 2010) and apixaban (Agrawal, Jain, & N Dikshit, 2012) act by inhibiting factor Xa production in the intrinsic and extrinsic coagulation cascades, while dabigatran (Ahrens et al., 2010) has direct inhibition on both fee and clot-bound thrombin. Time to reach the maximum plasma levels after oral intake is 2-4 hours, 3-4 hours and 1.5 hours, their half-lives is 7–13 hours, 10–14 hours, and 14-17 hours; bioavailability is 80-100%, 50%, and 7.2% respectively for rivaroxaban, apixaban and dabigatran. Rivaroxaban and apixaban do not induce cytochrome-P-450 (CYPP450) enzymes and so they are less likely to be affected by other drugs and foods (Jacomella et al., 2013). The dabigatran etexilate, the

prodrug dabigatran, is rapidly activated to dabigatran in the liver after oral administration. The metabolism of dabigatran, a substrate of a P-glycoprotein, is significantly influenced by P-glycoprotein inhibitors, quinine / quinidine and verapamil. The kidneys eliminate 80% of the dabigatran after hepatic activation (Jacomella et al., 2013).

High anticoagulant efficacy of oral vitamin K antagonist warfarin, which has been used for many years, is known in thrombotic diseases. However, it has significant limitations due to its high bleeding risk and high interaction with other drugs and nutrients, necessity of continuous monitoring of its effect during its use (Chan & Weitz, 2019; Chaudhary et al., 2019; Jacomella et al., 2013). Moreover, INR target level desired to be held between 2.0 and 3.0 during warfarin treatment is infrequently achieved more than 65% of patients (Chaudhary et al., 2019). In addition to their similar activity with warfarin, NOACs have favorable properties which are advantageous; speadly inception action, short half-life, low risk of bleeding and no need for close monitoring, and limited interactions with drug and food compared to warfarin (Chaudhary et al., 2019).

Acute gastrointestinal (GI) hemorrhage is the most frequent side effect caused by oral anticoagulant therapy. Based on the increased use of anticoagulants worldwide, the proportion of GI side effects also increases. Oral agents directly associated with topical cytotoxic effects can often cause GI intolerance or bleeding. In addition, in an experimental study has showed that FXa inbitors (rivaroxaban and apixaban) is less cytotoxic than dabigatran and warfarin (Kubat,

Gurpinar, Karasoy, & Onur, 2018). Similarly, a previous study using oral anticoagulants demonstrated higher GI intolerance with dabigatran compared to warfarin (Staerk et al., 2015).

A disadvantage limiting the utilization of NOACs is the paucity of an agent that could antagonize its effects in cases of acute bleeding or necessity of urgent surgery. Idarucizumab in patients given dabigatran and andexanet alpha in patients given factor Xa inhibitors have recently been approved for reversal (Chaudhary et al., 2019). Further studies on the effects of specific reversal agents for NOACs are needed to increase their use in clinical practice.

2. PERIPHERAL ARTERIAL DISEASE, CAROTID ARTERY STENOSIS AND CORONARY ARTERY DISEASE AND NOACS

In the PIONEER-AF (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial, groups of atrial fibrillation (AF) patients undergoing PCI using warfarin-clopidogrel-aspirin, rivaroxaban 15 mg-clopidogrel and low-dose rivaroxaban (2.5 mg) - clopidogrel-aspirin were randomized (Gibson et al., 2016). When compared to triple treatment of VKA plus DAPT, dual treatment with clopidogrel plus NOAC showed an almost 50% decrease in bleeding risk and similar rates for major advers cardiovascular events (MACE).

In the REDUAL-PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial, a P2Y12 inhibitor-dabigatran (either 110 or 150 mg) or a P2Y12 inhibitor-warfarin-aspirin combinations were randomized (Cannon et al., 2017). In both dabigatran-based groups, frequency of hemorrhage event was significantly lower compared to the group given VKA, and there was no significant increase in MACE.

In the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 51) study, placebo-controlled, double-blind study published in early 2012, patients with a new onset acute coronary syndrome were received either twice daily 2.5 mg or 5 mg rivaroxaban or placebo plus ASA which in 93% was combined with a thienopyridine for an average of 13 months. In this study, both remedies of rivaroxaban either 2.5 and 5 mg doses twice daily provided a significant reduction in the death from cardiovascular causes, death from any cause, myocardial infarction, or stroke (Mega et al., 2012). In addition, risk of stent thrombosis significantly reduced by a large amount with rivaroxaban. Not 5 mg of rivaroxaban twice daily but 2.5 mg rivaroxaban twice daily decreased the risk of mortality related to cardiovascular or any other reasons compared to placebo and the results obtained with these different doses of rivaroxaban were

significantly different (Mega et al., 2012). The incidence of intracranial and major bleeding but not lethal hemorrhagical or other adverse events was also significantly increased with rivaroxaban compared to plasebo. Fatal hemorrhage with rivaroxaban 2.5 mg twice daily appeared significantly less than 5 mg twice daily regimen (Gibson et al., 2011; Mega et al., 2012). Therefore, when used with low-dose FXa inhibitor regimens antiplatelet therapy have a better benefit-risk profile than higher dose regimens.

The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic and Safety Events**) (**phase III**)**) trial compared the use of placebo and 5 mg apixaban twice daily combined with antiplatelet drugs in patients having current ACS. There was no significant difference in terms of primary outcomes regarding cardiovascular mortality, myocardial infarction and ischemic stroke between the apixaban and placebo group. In addition, an increased rate of a significant major hemorrhagical events (intracranial and lethal hemorrhage) was seen in the group given apixaban. Therefore, the APPRAISE-2 trial was prematurely stopped (Alexander et al., 2011).

Different bleeding rates between APPRAISE-2 and ATLAS ACS 2-TIMI 51 were not well explained owing to the differences in the patient characteristics and medication regimens in the two studies. The occurrence of these outcomes may be due to the fact that the patients in APPRAISE-2 are older, the comorbit diseases are more frequent (De Caterina et al., 2012), and the FXa inhibition doses of the agents used in both trials are different (Jacomella et al., 2013).

The RE-DEEM (Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome) trial is the only dose-finding (phase II) study to assess the safe and efficacy dose of oral direct thrombin inhibitor dabigatran etexilate. In the trial, patients receiving dual platelet inhibitors had increased dose-dependent bleeding events with twice daily 110 and 150 mg dabigatran etexilate. Although the study was not powered in respect to prevention of cardiovascular death, nonfatal myocardial infarction or nonhemorrhagic stroke, diminished event rates were observed in patients receiving high doses of dabigatran compared to low-dose dabigatran etexilate and placebo (De Caterina et al., 2012; Oldgren et al., 2011).

COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial is a Phase III study conducted to determine the safety and effectiveness of rivaroxaban in patients with stable CAD and / or PAD (Bosch et al., 2017; Eikelboom et al., 2017). In the study, a total of 27.395 patients who received 2.5 mg rivaroxaban plus 100 mg aspirin, 5 mg rivaroxaban alone, or 100 mg aspirin alone were compared in a 1: 1: 1 ratio (Eikelboom et al., 2017). In the ASA plus rivaroxaban group primary outcomes and secondary composite outcomes were significantly decreased compared to the ASA group alone. The primary outcomes were similar between the only rivaroxaban group and the only ASA group. In addition, the combination regimen was superior to rivaroxaban alone in preventing MACE (Eikelboom et al., 2017). Both combination regimen and

rivaroxaban only were significant increased the frequences of major hemorrhage events in compared with aspirin. However, intracranial, critical or lethal organ hemorrhage was found alike among the groups (Eikelboom et al., 2017). Low dose rivaroxaban plus aspirin therapy revealed associated with decreased overall mortality. The rivaroxaban + ASA group showed consistent benefits in subgroups with either CAD or PAD patients compared to the ASA group alone. In patients with stable PAD included in the COMPASS trial, twice daily 2.5 mg rivaroxaban + ASA provided significant benefit in decreasing major adverse events of the limb or major amputation or MACE in compared to ASA alone (S. Anand & Investigators, 2017; S. S. Anand et al., 2018). There was an increase in major hemorrhage in the rivaroxaban + ASA group with respect to the ASA only group, but critical or lethal organ hemorrhage was alike between the two groups (S. Anand & Investigators, 2017).

ESC / ESVS gidelines recommends NOAC in PAD and CHA2DS2-VASc score≥ = 2. If the risk of hemorrhage after endovascular revascularization is low compared to the risk of stent / graft occlusion, NOAC should be given for at least one month as well as ASA or clopidogrel. If the risk of hemorrhage is high compared to the risk of stent / graft occlusion, NOAC alone regimen should be considered (Victor Aboyans et al., 2017).

For asymptomatic and symptomatic CAAD, long-term use of single anti-platelet therapy (aspirin) is recommend by the European guidelines (V Aboyans et al., 2018). Besides, in patients undergoing

carotis artery endarterectomy (CEA) and carotis artery stenting (CAS) dual antiplatelet therapy is recommended (V Aboyans et al., 2018). Preoperative dual antiplatelet therapy in patients undergoing CEA reduces neurological events by 39% relative to aspirin alone, but increases the rate of hemorrhage-related reoperations (Jones et al., 2016). The use of DAPT is related to increase in all-cause mortality (Alcocer et al., 2014).

Regarding mild-to-moderate asymptomatic carotid artery stenosis, the COMPASS trial randomized patients with CAAD into 3 groups as twice daily 5 mg rivaroxaban, twice daily 2.5 mg rivaroxaban plus daily 100 mg aspirin and daily a single dose of 100 mg aspirin regimen (S. S. Anand et al., 2018). In this subgroup of patients, the results were alike with results of PAD arm of the COMPASS trial S. S. Anand et al., 2018). Specifically, CAAD patients treated with a combined use of aspirin and low-dose rivaroxaban had a lower frequency of MACEs than those treated with aspirin alone and the rates of hemorrhagical events was not different between both groups (S. S. Anand et al., 2018).

In randomized clinical trials, when NOACs were used alone or use together with antiplatelet therapy, low-dose use was related to lower bleeding rates without loss of efficacy relative to standard doses (Chan & Weitz, 2019). Thus, the findings of the COMPASS study with CAD or PAD patients support the idea that adding low-dose rivaroxaban to aspirin is better than rivaroxaban or aspirin alone to prevent of atherothrombosis and improve clinical findings.

VOYAGER PAD is a phase III, double-blind, randomized, placebo-controlled trial to define and design the safe and effective of dual-pathway therapy approach to ASA alone to reduce thrombotic vascular events after peripheral revascularization procedures including either infrainguinal surgical or interventional procedures with or without stents. In this study, the addition of 2.5 mg rivaroxaban twice a day to aspirin in patients with symptomatic PAD who underwent lower limb revascularization significantly reduced the compound results of ALI, amputation of vascular etiology, MI, ischemic stroke, or CV death. In addition, hemorrhage events tended to increase compared to the ASA group, but did not differ statistically (Capell et al., 2018; Bonaca et al., 2020).

It is evident that combination dual antiplatelet therapy with a new oral anticoagulant agent increases the risk of major and intracranial hemorrhage and this effect is dose-dependent. The PAD patients being generally older and more vulnerable to bleeding risk usually have a rough disease course complicated with atherosclerosis itself and its consequences. Regarding the ATLAS ACS 2-TIMI 51 and COMPASS trials, there is enough evidence to suggest that single antiplatelet therapy plus low dose rivaroxaban is related to lower risk for atherosclerotic events in patients with CAD or PAD.

3. CONCLUSION

As a result, atherothrombosis is usually poorly controlled by antiplatelet therapy alone. The addition of DOACs to antiplatelet therapy is promising for the safety and effectiveness of treatment. Dual pathway inhibition is a promising regimen which provides clear clinical benefit in selected patients of PAD and stable CAD in order to reduce major atherosclerotic events but careful consideration should be given to combine antiplatelet agents with low dose rivaroxaban to reduce hemorrhagic complications. Further research is needed to provide guide for optimum medical compositions and doseges in order to reduce the risk of major bleeding complications.

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CHAPTER 7

HERITABLE DISORDERS ASSOCIATED WITH TGFβ SIGNALING

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INTRODUCTION

Extracellular matrix (ECM) and associated proteins have many mechanical, chemical and biological functions including cell to cell communication, cell proliferation, migration, cell differentiation, development, and survival. ECM molecules bind and regulate several growth factors, such as transforming growth factor β (TGFβ). TGFβs are a family of soluble cytokines, and they serve as multifunctional regulators in myriad cellular mechanisms for instance cell differentiation, proliferation, recognition, adhesion, embryonic development and migration. TGFβ signaling pathway alterations are found in several diseases such as cardiovascular, fibrotic, reproductive, wound healing disorders and cancer. TGFβ upregulates several genes required for the elastic fibers, such as fibronectin, LTBPs, ELN, LOXs and FBLN5. Several heritable connective tissue disorders in consequence of mutations in ECM proteins and TGFβ signaling pathway components result in altered TGFβ signaling. We reviewed heritable connective tissue disorders related with TGFβ signaling including Marfan syndrome (MFS), as a consequence of fibrillin-1 mutations, Loeys-Dietz Syndrome (LDS), as a consequence of transforming growth factor receptor 1(TGFBR1) and transforming growth factor receptor 2 (TGFBR2) and Urban-Rifkin-Davis syndrome (URDS), as a consequence of latent TGFβ binding protein (LTBP4) mutations. We discussed and compared the mutational spectrum, clinical presentation and molecular aspects of each disease and we focused on and compared the mechanisms of TGFβ signaling

pathways in each disease. Understanding the disease etiology and molecular and physiological mechanisms can improve diagnosis and the development of molecularly targeted treatment.

1. EXTRACELLULAR MATRIX

The extracellular matrix (ECM) elements are collagen fibers, microfibrils, elastin, proteoglycans and glycoproteins, provides structural support in all tissues and organs in the body. In addition to the several roles in cell-cell communication, cell proliferation, migration and development, the ECM also stores growth factors and cytokines (Naba et al., 2012).

1.1. Elastic fibers

Connective tissues' (including arteries, lungs and skin) essential components are called elastic fibers that are found in the extracellular matrix (Kielty et al., 2006). The structural and mechanical roles of elastic fibers in connective tissues are to give elastic properties and flexibility to these tissues (Nistala et al., 2010).

1.2. Composition of elastic fibers

Elastin and microfibrils are two major pieces of elastic fibers and many accessory molecules also interact with elastin and microfibrils (Baldwin et al., 2013).

1.3. Elastin

Elastin composes the most important part of the elastic fibers and it is located on chromosome 7 (Baldwin et al., 2013). The secreted form, tropoelastin has hydrophobic and cross-linking domains (Dyksterhuis et al., 2010) and tropoelastin is secreted from elastogenic cells (Baldwin et al., 2013).

1.4. Fibrillin

Fibrillin is the crucial component of the microfibril scaffold, which provides a template for elastin deposition. Piha-Gossack and his colleagues (2012) Fibrillins are huge extracellular glycoproteins, which have great amount of cysteine, and the fibrillin family has three fibrillin genes in humans, fibrillin-1, fibrillin-2 and fibrillin-3 (Baldwin et al., 2013).

The most predominant fibrillin is fibrillin-1, and its gene is localized on chromosome 15. Fibrillin-1 is expressed all the time, responsible for microfibril homeostasis; however, the extensive expression of fibrillin-2 and fibrillin-3 happens while development (Charbonneau et al., 2010; Zhang et al., 1994). Charbonneau (2010) found that the interior parts of microfibrils with fibrillin-1 might be made from fibrillin-2. Fibrillin-1 is indicated to have crucial roles in vascular development in mouse models. Aortic aneurysm is death reason for FBN-$1^{-/-}$ mice, while FBN-$2^{-/-}$ mice have the healthy vascular development (Carta et al., 2006).

1.5. Accessory molecules

Several microfibril and elastic fiber related accessory molecules have been determined based on functional biochemical and morphological analyses. The microfibril-related molecules are listed below: (Baldwin et al., 2013)

- a disintegrin and metalloprotease with thrombospondin type-I motif (ADAMTS) and ADAMTS-like proteins
- microfibril-associated glycoproteins (MAGPs)
- latent TGFβ binding proteins (LTBPs),
- fibulin 3-5
- lysyl oxidase (LOX) and lysyl oxidase-like 1 (LOXL1)

The ADAMTS superfamily consists zinc metalloproteases and ADAMTS-like (ADAMTSL) proteins, which have roles in ECM deposition, microfibril biology and morphogenesis (Hubmacher et al., 2015). ADAMTSL members only have multiple thrombospondin type 1 repeats (TSRs), whereas ADAMTS family members have disintegrin-like and a cysteine-rich modules in addition to a single TSR (Baldwin et al., 2013). ADAMTS-10 and ADAMTSL 2-6 are important in microfibril biology (Hubmacher et al., 2015). The association between ADAMTSL-5 and fibrillin-1 and fibrillin-2 help colocalization with microfibrils (Bader et al., 2012).

MAGP-1 can associate with elastin and possibly help the elastin deposition on microfibrils (Jensen et al., 2001) and can also regulate of TGFβ signaling by binding TGFβ and BMP-7 (Weinbaum et al., 2008). MAGP-1 might also affect fibronectin-mediated microfibril deposition by interacting with fibronectin (Werneck et al., 2008). MAGP-2 was found to colocalize with microfibrils in several tissues (Lemaire et al., 2007; Gibson et al., 1998), however, MAGP1$^{-/-}$ mice demonstrated normal microfibrils and elastin, indicating that it is not crucial component of elastic fiber assembly (Craft et al., 2010). Lemaire and colleagues (2007) found that overexpression of MAGP-2 can enhance elastic fiber formation.

The LTBPs (LTBPS 1-4) are giant glycoproteins, and they have several domains including cbEGF and TB domains similar to fibrillins. LTBPs 1-4 are expressed in numerous tissues such as heart, lung, and ovary (Piha-Gossack et al., 2012; Todorovic et al., 2005). The third TB domains of LTBPs bind the small latent complex (SLC) of TGFβ comprising the latency-associated peptide (LAP) and the tightly but non-covalently bound TGFβ growth factor (Gleizes et al., 1996) to form the large latent complex (LLC) and also regulate the bioavailability of TGFβ (Todorovic et al., 2005; Gleizes et al., 1996). The fibrillin-1 and the fourth TB domain of LTBPs cooperation ensures the sequestration of the LLC to fibrillin microfibrils, which therefore they regulate, TGFβ activity too (Saharinen et al., 1996). Fibronectin is needed for LTBP-1 and LTBP-4 deposition into the ECM (Reber-Muller et al., 1995).

Fibulins are extracellular glycoproteins including fibulin 1-5 (Yanagisawa et al., 2010). Fibulin-4 and fibulin-5 can interact with LOX and LOX-like (LOXL) enzymes and fibrillin-1, and these interactions were implicated in elastin crosslinking and deposition onto microfibrils (Baldwin et al., 2013). Fibulin-3, -4 and -5 have important roles in the elastic fiber assembly (Yanagisawa et al, 2010). In addition, one likely role of fibulin-4 is to help sequestration of LTBPs (Ono et al., 2009). Fibulin-5 is a regulator of the deposition of elastin onto microfibrils (Zheng et al., 2007).

The five LOX family members are LOX and LOXL1-4 (Molnar et al., 2003). They oxidatively deaminate the peptidyl lysine residues, which is the part of elastin to form allysine, a reactive aldehyde. Three allysine and one lysine side chains automatically compress to make tetrafunctional desmosine and isodesmosine crosslinks to form insoluble elastin (Molnar et al., 2003). The N- terminal regions of LOX family members provide specificity to the extracellular LOX enzymes (Baldwin et al., 2013).

2. TGFβ SIGNALING

2.1. TGFβ signaling and TGFβ receptor system

TGFβs are a family of soluble cytokines, and they serve as multifunctional regulators in myriad cellular mechanisms such as cell differentiation, proliferation, recognition, apoptosis, adhesion and embryonic development (Santibanez et al., 2011). TGFβ also

modulates ECM structure and composition. TGFβ has three isoforms: TGFβ1, TGFβ2, and TGFβ3, each synthesized as homodimeric proteins with a mass of 75 kDa (Annes et al., 2003), and cut by a furin protease to the mature TGFβ and its propeptide, also known as the latency-associated peptide (LAP). The LAP and TGFβ form a small latent complex (SLC) by non-covalent bonds. TGFβ remains inactive in this form. The LAPs form large latent complexes (LLCs) with one of the LTBPs (LTBP1, -3 or -4) by disulfide bonds. Most cells secrete TGFβs in LLC form. Consistently, LTBPs are known to help the correct bond formation and secretion of TGFβ (Saharinen et al., 1999). LTBPs promote the incorporation of different TGFβs into the ECM. TGFβ signaling pathway alterations are found in several diseases such as cardiovascular, fibrotic, reproductive, wound healing disorders and cancer (Santibanez et al., 2011).

2.2. Canonical TGFβ signaling pathway

Annes and colleagues (20003) found that TGFβ can be triggered by delivered from the LAP by several systems, including proteolysis and low pH. After activation, TGFβ binds to a TGFβ receptor (Wrana et al., 1994). Three types of TGFβ receptors exist. Type 1 (TGFBR1) and type 2 (TGFBR2) receptor are the main TGFβ canonical pathway component. Type 3 receptor (TGFBR3) serves as an accessory receptor by binding TGFβ and bringing it to the TGFBR1 and TGFBR2 (Wrana et al., 1992).

Binding of TGFβ to dimeric TGFBR2 that induces autophosphorylation triggers the signaling. This autophosphorylation recruits a homodimer of TGBFR1 and after ligand-receptor complex is formed. Then, TGFBR1 is activated by TGFBR2 by transphosphorylation (Wrana et al., 1994). The kinase domain of the activated TGFBR1 triggers the downstream signaling by phosphorylation of receptor-associated SMAD proteins (R-SMADs; SMAD 2 and 3), then undergo formation of complexes with the co-operating SMAD (Co-SMAD), SMAD4. After activation, SMAD complexes are translocated into the nucleus and regulate gene expression (Moustakas et al., 2001). The inhibitory (I-SMAD) SMAD6 and SMAD7 compete with the R-SMADs for receptor or Co-SMAD binding, and thus negatively regulate TGFβ signaling (Shi and Massague, 2003). Imamure and colleagues (1997) found that SMAD6 inhibits TGFβ signaling by binding to TGFBR1 and repressing the phosphorylation of R-SMAD proteins. Another mechanism is to reduce the nuclear translocation (Hata et al., 1998). SMAD7 conducts the inhibition of TGFβ signaling by the ubiquitination and degradation of TGFBR1 and TGFBR2 as a result of the release of SMURF proteins (Wicks et al., 2006; Ebisawa et al., 2001).

1.6. Non-canonical TGFβ signaling pathway

Tumor necrosis factor receptor-associated factor 6 (TRAF6) connects with the TGFBR1 (Sorrentino et al., 2008) and it recruits and triggers TGFβ associated kinase 1 (TAK1) that causes an activation of p38 MAPK by phosphorylation (Yamashita et al., 2008). The other non-

canonical signaling pathways triggered in response to TGFβ including extracellular-signal regulated kinase 1 and 2 (ERK1/2) c-Jun N-terminal kinase (JNK) (Yamashita et al., 2008), and phosphoinositide 3-kinase-Akt (PI3KK-Akt) (Wilkes et al., 2005). Additionally, the canonical and non-canonical pathways cross-talk with each other and have different effects.

3. HERITABLE DISORDERS ASSOCIATED WITH TGFB SIGNALING

TGFβ upregulates several genes required for the elastic fibers. The regulation could be either transcriptional as in the case of fibronectin, *LTBPs*, *LOXs*, and *FBLN5* or post-transcriptionally in the *ELN* and *FBN1* gene. Van Rooij and colleagues (2008) found that one possible mechanism how *ELN* and *FBN-1* is regulated at the post-transcriptional level is through the repression of the miR29 family by TGFβ. miR29 binding sites have been identified in many mRNAs of elastic fiber genes such as *ELN*, *FBN1* and *LTBP1* (Urban et al., 2014).

Many heritable connective tissue disorders caused by mutations in ECM proteins and TGFβ signaling pathway elements conclude in changes in TGFβ signaling (Table 1). Fibrillin-1 mutations cause Marfan syndrome (MFS). Increased TGFβ signaling was found in the lung of an MFS mouse model (Neptune et al., 2003). In these MFS mice, aortic aneurysms were also improved with an anti-TGFβ antibody, indicating enhanced TGFβ signaling was a major factor in

MFS pathogenesis (Habashi et al., 2006). Increased non-canonical TGFβ signaling appears to devote to cardiovascular defects in MFS mice whereas canonical TGFβ signaling is thought to be protective (Holm et al., 2011).

The *LTBP4* mutations cause autosomal recessive cutis laxa type 1 (ARLC1C) patients and dermal fibroblasts have increased TGFβ activity (Urban et al., 2009). Loeys- Dietz syndrome (LDS) patients with TGFBR1 and TGFBR2 mutations also showed increased TGFβ signaling as well as enhanced collagen and connective tissue growth factor (CTGF) expression (Loeys et al., 2005). Table 1 summarizes the inherited diseases associated with TGFβ signaling. We will discuss Marfan syndrome, LDS and URDS in more detail in upcoming sections.

Table 1. Disorders associated with TGFβ signaling

Disease	**Mutations**	**Clinical presentations**
Loeys-Dietz Syndrome (LDS)	TGFBR1 and TGFBR2	Severe vascular effects, ocular, skeletal and craniofacial abnormalities
Marfan Syndrome (MFS)	FBN-1	Aortic aneurysms, skeletal and ocular abnormalities
ADCL	ELN	Loose skin, aortic stenosis, pulmonary emphysema
ARLC1/URDS	LTBP4	Developmental delay, redundant, inelastic skin
Arterial tortuosity syndrome	SLC2A10	Cutis laxa with tortuous arteries
Ehlers-Danlos syndrome	FN	Hyperelastic skin, atrophic scarring

3.1. Marfan syndrome

Marfan syndrome (MIM 154700) is a heritable connective tissue disorder with a variety of clinical characteristics and it is diagnosed during childhood. The first MFS case was reported in 1896 (Marfan et al., 1896). We discussed the clinical presentation, mutational spectrum and molecular mechanisms of MFS in the following section.

3.1.1. Clinical presentation

MFS has diverse clinical including cardiovascular, ocular and skeletal (Pyeritz et al., 2000). In addition to these common characteristics, skin, lung, fascia and adipose tissues may also be affected in MFS patients (Pyeritz et al., 2000). Loeys and colleagues (2010) stated that marfan syndrome is diagnosed based on Ghent nosology when a patient has a FBN1 gene mutation and having either aortic root enlargement or ectopia lentis. MFS can be diagnosed right after birth or at the age of 30s (Pyeritz et al., 2000). The clinical characteristics are summarized below:

Cardiovascular characteristics: Cardiovascular manifestations are the most important mortality and morbidity causes in Marfan syndrome (Dietz et al., 2017) and around 80 % of the patients have cardiovascular anomalies (Jason C. et al., 2014). Aortic dilatation, aortic dissection, pulmonary artery dilatation and valvular abnormalities including mitral and tricuspid valve are the most

common cardiovascular hallmarks of Marfan syndrome patients (Dietz et al., 2017).

Skeletal characteristics: The skeletal clinical characteristics of marfan syndrome patients include excessive growth of long bones and joint laxity, arachnodactyly, dolichostenomelia, pectus excavatum, pectus carinatum and scoliosis (Dietz et al., 2017).

The facial clinical characteristics are enophthalmos, malar hypoplasia and micrognathia (Dietz et al., 2017).

Ocular characteristics: Myopia is the most typical clinical characteristics of Marfan syndrome patients (Dietz et al., 2017). 60% of the Marfan syndrome patients have ectopia lentis (Dietz et al., 2017). Detached retinas, glaucoma and cataract are high risk for MFS patients (Dietz et al., 2017).

3.1.2. Mutational spectrum

MFS is an autosomally-inhereited disease as a result of the FBN1 gene mutations with the incidence of 1 in 5,000- 1:10,000 individuals (Pyetritz et al., 1979). 25% of MFS patients have de novo mutations. Until now around 1000 FBN1 gene mutations have been foundin marfan syndrome patients. FBN1 mutations include missense, frameshift, splicing, nonsense, in-frame deletions and insertions and premature termination codons (PTCs) (Collod-Beroud et al., 2003). Genotype-phenotype correlations of MFS are unclear (De Backer et

al., 2018) and more research is needed. While missense mutations resulted in ectopia lentis with higher risk (Faivre et al., 2007), nonsense mutations resulted in more severe clinical characteristics (Takeda et al., 2018).

3.1.3. Molecular mechanisms

To date, several molecular mechanisms of MFS have been found based on disease mouse models and recombinant FBN1 studies (Baldwin et al., 2013). FBN1 gene mutations usually cause alterations in disulphide bonds or calcium-binding sequences in cbEGF domains and these alterations lead to structural changes in microfibril and elastic fiber assembly (Robinson et al., 2006). FBN1 gene proteolytic susceptibility is an important mechanism o MFS (Ashworth et al., 1999). Matrix metalloproteninases (MMPs) were upregulated in MFS patients and MFS animal models (Chung et al., 2007).

Increased TGFbeta signaling has been found in the Marfan syndrome animal models (Neptune et al., 2003 and Loeys et al., 2005). Habashiand colleagues (2011) found an increased non-canonical TGFbeta signaling in Marfan mouse models. Abnormal FBN1 gene mutations cause dominant-negative mechanisms. Decreased levels of microfibrils are the most important aspect of the marfan syndrome (Dietz et al., 2017).

The other molecular mechanism of Marfan syndrome is haploinsufficiency.

3.2. Loeys-Dietz Syndrome

LDS (OMIM 609192) is a rare, autosomally-inherited connective tissue disorder with common systemic inclusion and it is first described in 2005 (Loeys et al., 2005).

3.2.1. Clinical presentation

The clinical characteristics can be mild to severe including vascular, skelatal, craniofacial, cutaneous and ocular findings (Loeys et al., 2005). Some clinical characteristics of LDS are in common with Marfan syndrome, but there are also some different clinical characteristics. The common characteristics are pectus excavatum, aortic root aneurysm, scoliosis and arachnodatyly (Loeys et al., 2005). The clinical characteristics that differ from Marfan syndrome are arterial aneurysms, cleft palate or cleft uvula and hypertelorism (Loeys et al., 2005). Clinical characteristics are summarized below:

Cardiovascular characteristics: Aortic root dilatation is the most prevalent cardiovascular characteristics of LDS that can result in aortic dissection.

Skelatal characteristics: Most common skeletal characteristics are joint laxity, pectus excavatum, scoliosis, arachnodactyly and osteoarthritis.

Craniofacial characteristics: wide set eyes, cleft uvula

Cutaneous characteristics: velvety skin and dystrophic scars

Allergic/inflammatory characteristics: food and seasonal allergies, asthma

Ocular characteristics: Blue sclerae and myopia

3.2.2. Mutational spectrum

The inheritance of LDS is autosomal dominant and while 25% of LDS patients have familial mutations, 75% of LDS patients have de novo mutations. De novo mutations usually resulted in more severe clinical consequences; however, familial mutations resulted in milder clinical consequences. It is subdivided in 5 different classes based upon the genetic mutations in five genes that are important in TGFβ pathway including TGFBR1, TGFBR2, SMAD3, TGFB2, and TGFB3 (Table 2). (Loeys et al., 2008). The classification of LDS also shows the severity of the disease, LDS1 is the most severe type and LDS5 is the least severe type. LDS1 patients show more severe clinical characteristics when compared to LDS5 patients (Loeys et al., 2008). MacCarrick and colleagues (2014) found that Loeys-Dietz syndrome is diagnosed based upon the 2 criteria: finding a mutation in either of the following genes: TGBFR1, TGFBR2, SMAD3, TGFB2 and TGFB3 and having aortic root enlargement or dissection or having skeletal, vascular, craniofacial and cutaneous clinical characteristics. Because LDS is genetically heterogeneous disease, the genotype-phenotype correlations are unclear. Uncovering the genotype-

phenotype correlations may help finding the treatment of the disease specific to a patient (et al., 2019).

Table 2. Loeys-Dietz Syndrome Classes

Gene	**LDS class**	**Clinical characteristics**
TGFBR1	LDS1	Aortic root aneurysm, aortic dissection, hyoertelorism, cleft uvula, pectus deformity
TGFBR2	LDS2	Aortic root aneurysm, aortic dissection, hyoertelorism, cleft uvula, pectus deformity
SMAD3	LDS3	Osteoarthritis (van de Laar et all, 2011), milder cardiovascular characteristics, hypertelorism, micrognathia, cleft palate, scoliosis
TGFB2	LDS4	Milder systemic characteristics, Hypertelorism, arterial tortuosity, arterial aneurysms, dural ectasia,
TGFB3	LDS5	Hypertelorism, arterial tortuosity, arterial aneurysms, dural ectasia,

3.2.3. Molecular mechanisms

LDS patients have enhanced TGFβ signaling (Loeys et al., 2005). The amount of elastin and the union between elastin and smooth muscle cells were decreased based on the conclusions of histological analysis (Loeys et al., 2005).

It was found that abnormal TGFβ signaling was related to abnormalities in pulmonary alveolarization and primary spontaneous pneumothorax. In addition, the increased TGFβ signaling causes abnormalities in ECM and this result in clinical characteristics of the LDS.

3.3. Urban-Rifkin-Davis Syndrome (URDS)

3.3.1. Clinical presentation

Cutix laxa (CL) is a rare connective tissue disorder, defined as elastic fiber abnormalities and there are two types of CL including acquired and inherited (Berk et al, 2012). CL patients have loose, redundant and inelastic skin and several clinical characteristics. The CL types are summarized in Table 3. The inherited types of CL consists of autosomal dominant CL (AD), autosomal recessive (AR) CL and X-linked recessive CL (XLR) inherited forms (Proud et al., 1996). The cutis laxa genes identified so far are A*LDH18A1, ATP6V0A2, ATP7A, EFEMPS/FBLN4, ELN, FBLN5, LTBP4, PYCR1* and *RIN2*.The other name of X-linked cutis laxa is Occipital Horn Syndrome (OHS), caused by the a copper-transporting ATPase (*ATP7A)* gene mutations

and patients have general cutis laxa characteristics including long philtrum, beaked nose and high forehead. The other clinical characteristics include urethral and bladder abnormalities, congenital hydronephrpsis and skeletal abnormalities (Mohamed et al., 2014).

Autosomal dominant cutis laxa is the milder type of cutis laxa and ELN gene or the fibulin-5 (FBN5) gene mutations are responsible for the ADCL phenotype and the clinical characteristics are sagging, inelastic skin, hernias, cardiovascular abnormalities and emphysema (Callewaert et al., 2011). The disease mechanism of ADLC is dominant-negative affect on elastin deposition, which resulted in decreased levels of elastin (Callewaert et al., 2011). Callewaert and colleagues (2011) also found that increased TGFbeta signaling have also been found in ADCL patients.

Autosomal recessive cutis laxa (ARCL) is the severe and most prevalent group of cutis laxa and has several subtypes including Fibulin-5 (FBN5) mutations are responsible for the ARCL type 1A (ARCL1A) (Elahi et al., 2006, EGF-containing fibulin-like extracellular matrix protein 2 gene (EFEMP2) or fibulin-4 (FBLN4) gene mutations are responsible for the ARCL type 1B (ARCL1B) (Dasouki et al., 2007), URDS (ARCL1C), caused by mutations in LTBP4 gene (Urban et al., 2009), ARCL type 2, caused by LTBP4 mutations. ARCL type 2 is the milder type of autosomal recessive cutis laxa has 2 subtypes including ARCL type 2A and ARCL type 2B. ATP6V0A2 mutations cause ARCL type 2A (Fischer et al.,

2012;) and PYCR1 mutations cause ARCL type 2B (Dimopoulou et al., 2013).

Gerodermia Osteodysplastica (GO) is another type of ARCL type 2 and the Golgi causes the disease, RAB6-interacting gene (GORAB) mutations (Hennies et al., 2008). RAB interactor 2 gene (RIN2) mutations cause macrocephaly, alopecia, cutis laxa, and scoliosis (MACS), also a subtype of ARCL2 (t et al., 2014).

The *LTBP4* mutations are implicated in patients with cutis laxa with pulmonary, gastrointestinal, musculoskeletal and dermal malformations and it is called Urban-Rifkin-Davis Syndrome. Later, it is also named as autosomal recessive cutis laxa type Ic (Urban et al., 2009). Some clinical characteristics are in common with MFS and LDS (Table 5), however, involvement of severe pulmonary, gastrointestinal, genitourinary and dermal abnormalities differentiate this disease from others (Urban et al., 2009). URDS is a clinically variable disorder and clinical characteristics are summarized below:

Skin: Generalized cutis laxa (Callewaert et al., 2016).

Craniofacial: Long philtrum, thin forehead, hypertelorism, wide suture or fontanels, depressed nasal bridge, periorbital swelling (Callewaert et al., 2016).

Pulmonary: Pulmonary emphysema, pneumonia, bronchiolitis, pulmonary hypertension, congenital hernia (Callewaer et al., 2016).

Gastrointestinal: Pyloric stenosis, sliding hernias, congenital hernias, hiatal hernia, rectal prolapse (Callewaert et al., 2016).

Genitourinary: Bladder divertcula, incomplete voiding, hydronephrosis, inguinal hernia (Callewaert et al., 2016).

Cardiovascular: Peripheral pulmonary artery stenosis, septal defecsts, atrial aneurysm, valvulae dysfunction, arterial tortuosity and aortic root widening (Su et al., 2015), pulmonary hypertension

Neurologic: Hypotonia (Callewaert et al., 2016).

Other: Ingual and umbilical hernias, postnatal growth delay, joint laxity (Callewaert et al., 2016).

3.3.2. Mutational spectrum

LTBP4 gene mutations are responsible for the ARCL1C/URDS (MIM613177) and the inheritance of the disease is autosomal dominant. 18 individuals from 14 families have been determined with URDS until now (Urban et al., 2009, Callewaert et al., 2013, Su et al., 2015, Ritelli et al., 2019).

URDS mutations types are frameshift, nonsense and splice site mutations; they cause premature termination codon and result in activation of nonsense-mediated mRNA decay (NMD) (Callewaert et al., 2013). One patient with a c.4238dupC pathogenic variant resulted

in truncated protein that partially escaped from NMD (Callewaert et al., 2013).

3.3.3. Molecular mechanisms

The lack of LTBP4 results in altered production of active TGFβ and disorganized elastic fibers (Callewaert et al., 2013). However the exact molecular mechanism of TGFβ signaling and ECM is poorly understood. (Urban et al., 2009). Stabilization of TGFβ receptors by LTBP4 and LTBP4 mutations caused decreased TGFβ signaling (Su et al., 2015).

CONCLUSION

ECM and associated proteins have many mechanical, chemical and biological functions such as cell-cell communication, cell proliferation, migration, cell differentiation, development, and survival. ECM molecules bind and regulate several growth factors such as TGFβ. TGFβ families have roles in cell proliferation, cell growth, inflammation, apoptosis and extracellular matrix production (Santibanez et al., 2011). In this review, we concentrate on the heritable connective tissue disorders associated with TGFβ signaling including MFS, LDS and ARCL1/URDS and we discussed and compared the clinical presentation, molecular mechanisms and mutational spectrums. The clinical characteristics of MFS, LDS and URDS are summarized in Table 3. There are some clinical overlaps in all diseases.

All connective tissue disorders we reviewed in this study have TGFβ signaling changes. Enhanced TGFβ signaling was found as a result of abnormal microfibril structure in MFS patients. Abnormal elastic fiber deposition in LDS patients may associate with increased TGFβ signaling. The abnormal synthesis of LTBP4 into the ECM in URDS patients leads to the enhanced TGFβ signaling and abnormal elastic fiber assembly. Further investigation is needed to figure out the exact molecular mechanisms of TGFβ. Solving the molecular mechanism of TGFβ in all diseases may help finding therapeutic intervention.

Although the genes of these diseases were identified recently, further research needed to solve the disease mechanisms and to determine therapeutic interventions. In addition, molecular insights into these diseases might be relevant to common, complex diseases.

Table 3. Clinical characteristics of MFS, LDS and URDS

Disease	**MFS**	**LDS-TGFBR1/TGFBR**	**LDS-SMAD3**	**LDS-TGFB2**	**LDS-TGFB3**	**LDS-SMAD2**	**URDS**
Ectopia lentis	+++	-	-	-	-	-	-
Tall stature	+++	+	+	++	+	+	-
Aortic root aneurysm	+++	++	++	++	+	+	_
Skin laxity	-	+	+	+	+	+	+++
Pulmonary artery stenosis	++	-	-	-	-	-	++
Joint laxity	+++	+++	+++	+++	+++	+++	++
Hyoertelorism	+++	-	-	-	-	-	++
Microretrognathia	++	-	-	-	-	-	+++
Arachnodactily	+++	++	++	++	++	++	-
Hypertelorism	-	+++	+++	+++	+++	+++	++
Arterial tortuosity	-	++	++	++	++	++	-
Mitral valve insufficiency	++	+	+	++	+	+	-
Arterial aneurysm	-	++	+	+	+	+	-
Osteoarthritis	+	+	+++	+	+	+	-
Cleft palate/bifid uvula	-	++	+	+	+	+	-
Long philtrum	-	-	-	-	-	-	+++
Gastrointestinal malformations	-	-	-	-	-	-	+++
Genito-urinary malformations	-	-	-	-	-	-	+++
Lethal bronchopulmonary dysplasia	-	-	-	-	-	-	+++

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CHAPTER 8

BEING A HEALTHCARE PROFESSIONAL IN DIALYSIS DURING COVID-19 PANDEMIC

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INTRODUCTION

Fatal effect potentials of epidemics experienced one after another in the past 20 year such as SARS (severe acute respiratory syndrome), MERS–CoV infection (Middle East Respiratory Syndrome Coronavirus) and Influenza have gradually increased the awareness of policy makers and the society. The COVID-19 pandemic, which started at the end of December 2019 and which is still continuing today, is defined as a phenomenon that is spread globally on a larger scale than all these epidemics (Tuncay, Koyuncu, & Özel, 2020).

In terms of the emergence process of COVID-19 pandemic; the first signals of the outbreak started when Wuhan Municipal Health Committee announced new pneumonia cases of unknown causes on December 31, 2019. On January 12, 2020, the coronavirus newly discovered by the World Health Organization (WHO) was temporarily named "2019-nCoV". This single-chain, positive-polar, enveloped RNA has been recognized as the seventh identified coronavirus (CoV) that can infect humans (Dikmen, Kına, Özkan, & İlhan; Jia Wang & Wang, 2020). On January 31, 2020, WHO announced that 2019-nCoV is an international emergency public health situation. On February, 2020, WHO named the virus that caused severe acute respiratory tract disease as "Coronavirus Disease-2019 (COVID-19)" and declared a pandemic, which means global epidemic. The word COVID-19 is coined from co' in 'corona', vi in 'virus' and d' in 'disease'. Although it is the same coronavirus type with SARSCoV and MERS-CoV, the origin of the genetically different COVID19 is unknown. However, it

is estimated that it originates from the Huanan Seafood Market (a wholesale fish and live animal market where different animal species are sold) in Wuhan, China's 11 million population city (Zhou et al., 2020). The disease is transmitted through droplets emanating from coughing and sneezing and from the surfaces that patients touch (through touching the eye, mouth and nose mucosa with hands) (Ministry of Health, 2020). It has been observed that average incubation period is 5-6 days (2-14 days) and that in some cases it can extend up to 14 days (Alıcı, Beyan, & Şimşek, 2020). The epidemic was first detected in Turkey on March 10, 2020 and as of 06.07.2020, 3.682.673 individuals were tested (polymerized chain reaction (PCR) method), COVID-19 was detected in 206.844 individuals and the number of individuals who lost their lives was reported as 5.241 (Covid19.saglik.gov.tr, 2020).

COVID-19 can cause clinical pictures in humans and animals coursing with various degrees of respiratory, enteric, hepatic, nephrotic and neurological involvements (Alıcı, Beyan, & Şimşek, 2020). It has been reported that 81% of COVID-19 cases have asymptomatic clinical picture (no or mild pneumonia), while 14% have severe disease clinical picture (for exp. dyspnoea, hypoxia or more than 50% lung involvement in imaging within 24 – 48 hours) and 5% have critical disease clinical picture (for exp. respiratory failure, shock or multiorgan dysfunction) (Z. Wu & McGoogan, 2020). The main symptoms at disease onset have been reported as fatigue, fever, dry cough, myalgia and dyspnoea, while less common

symptoms have been reported as nasal congestion, headache, runny nose, sore throat, vomiting and diarrhoea. In severe cases, dyspnoea and/or hypoxemia usually develop a week after onset and following this patients develop septic shock and Acute Respiratory Distress Syndrome (Çöl & Güneş, 2020).

Healthcare professionals are fighting at the forefront against COVID-19 infection. Healthcare professionals, who are directly interested in the diagnosis, treatment and care of patients are on the one hand making efforts to prevent the spread of the virus and on the other hand learning information, conducting scientific studies and frequently updating their approaches to patients (Lai et al., 2020). Infectious diseases are among the most common causes of occupational death among healthcare professionals (Sepkowitz & Eisenberg, 2005). In almost all infectious diseases, the places where contamination takes place the most are hospitals and other health institutions (Fessell & Cherniss, 2020; Styra et al., 2008). Therefore, the hygiene and personal protection rules of the working environment are a priority. For healthcare professionals, being infected with external infections in the hospital environment or being in the same environment with people diagnosed with COVID-19 increases mental symptoms (Kaya, 2020).

Four exposure levels have been defined according to the risks of employees' being faced with the virus. According to this classification, healthcare professionals are considered as the occupation group with the highest risk due to their close contact with

patients affected by COVID-19 (Alıcı, Beyan, & Şimşek, 2020). According to Ministry of Health data, 7428 healthcare professionals have been infected with COVID-19 (İstanbul Chamber of Medical Doctors, 2020). In addition to being a medical phenomenon, pandemic is also a social phenomenon that affects the individual and the society at many levels and causes disruptions. This is because as the perception of threat caused by infectious disease increases, individuals who experience panic and stress show different behaviours than usual. When faced with a condition the effects of which are unpredictable such as epidemic disease, individuals experience a sense of fear and panic (Karataş, 2020).

Healthcare professionals are exposed to both physical and psychological stress during this pandemic process (Lu, Wang, Lin, & Li, 2020; Zeng & Zhen, 2020). In the fight against this very serious epidemic disease, healthcare professionals are exhausted physically and they also suffer psychologically. They experience feelings of desperation, anxiety and fear because it is not known when this extraordinary situation will end and they are in the highest risk group for COVID-19 infection (Zeng & Zhen, 2020). Having too many cases and insufficient number of staff in health institutions is a factor that is usually common in pandemics and it can increase psychological stress (Porten, Faensen, & Krause, 2006). Working time is a factor that directly affects the severity of stress responses of healthcare professionals. As the working time in the relevant service of the hospital increases, the frequency of interaction with patients increases,

the load of clothing and equipment which are used to protect from contamination increases and these can be accompanied with increasing emotional exhaustion. Undoubtedly, the intensity of these processes can cause burnout symptoms in employees (Sasangohar, Jones, Masud, Vahidy, & Kash, 2020). In addition, healthcare professionals are also afraid to infect the virus to their families and loved ones when they come across critical patients (Lu et al., 2020). This situation triggers various psychological problems such as panic disorder, anxiety and depression (Pappa et al., 2020). It has been found that healthcare professionals are twice as likely to experience anxiety and depression than administrative staff (Lu et al., 2020).

This study was carried out to find out the Covid-19 knowledge and anxiety levels of healthcare professionals working in dialysis units during the COVID 19 pandemic process. In literature review, no studies were found on the Covid-19 knowledge and anxiety levels of healthcare professionals working in dialysis units. This study is thought to be important in terms of filling the gap in literature.

1. METHODS

1.1. Setting and Characteristics of the Study

This descriptive and cross-sectional study was carried out to find out the Covid-19 knowledge and anxiety levels of healthcare professionals working in dialysis units during the COVID 19 pandemic process.

1.2. Sample of the Study

The study was carried out between April 1 and 9, 2020. Data collection forms prepared in GoogleDocs program was sent online to dialysis technicians and the nurses in whatsapp group of Turkish Nephrology, Dialysis and Transplantation Nurses Association and they were asked to fill in the forms. 88 individuals who responded to the survey were included in the study.

1.3. Data Collection Instruments

The data were collected by using Personal Information Form prepared by the researchers and Coronavirus Anxiety Scale (CAS).

1.3.1. Personal Information Form

The form prepared by the researchers includes questions such as the participants' socio-demographic characteristics (age, gender, marital status, etc.), work information (years of working, unit they worked in and their job) and questions about COVID-19.

1.3.2. Coronavirus Anxiety Scale (CAS)

The scale developed by Lee (2020) is used to find out the level of anxiety related with COVID-19. Turkish validity and reliability study of the scale was conducted by Evren et al. (2020). 5-Likert type CAS scale has 5 questions and a single dimension. The scale is scored as "0" "Not at all", "1" "Rare, less than a day or two", "2" "Several days", "3" "More than 7 days" and "4" "Nearly every day over the

last two weeks". As the score from the scale increases, the level of anxiety also increases. Cronbach's Alpha value of the scale was reported as 0,80 (Evren et al., 2020). In the present study, Cronbach's Alpha value was found as 0,81.

1.4. Data Assessment

Numbers, percentage, mean, standard deviation, Mann Whitney U test, Kruskall Wallis and Pearson Correlation Coefficient were used in the assessment of the data obtained from the study. Statistical analyses were conducted with SPSS 25 program and significance in statistical analyses was taken as 0.05 (p-value).

1.5. Ethical Principles of the Study

The study was conducted in accordance with the principles of Helsinki Declaration of Human Rights. (2020/06 numbered) approval was taken from the Ethics Committee of a Foundation University and required permissions were taken from T. R. Ministry of Health Scientific Researches Committee (2020-05-23T13_10_15).

2. RESULTS

Table 1 includes sociodemographic characteristics and work information of the participants. Average age of the participants was 38.66±7.73, while their average years in the profession was 18.24±8.48, average years of working in the dialysis unit was 13.7±7.61 and average daily number of patients cared for was 42.7±27.69. 94.3% of the healthcare professionals were women, 75%

were married, and 61.4% had undergraduate degree. It was found that 83% of the participants were working as dialysis nurse, 77.3% were working in haemodialysis unit, the spouses of 19.3% were healthcare professionals, 25% had a chronic disease, 31.8% were smoking and 8% were using psychiatric medication.

Table 1. Sociodemographic Characteristics and Work Information of the Participants

		Ave±Sd	**Min-Max (Median)**
Age		38.66±7.73	20-52 (40)
Number of Children		1.34±0.95	1-4 (2)
Years in the Profession		18.24±8.48	1-32 (20)
Years of working in haemodialysis		13.7±7.61	1-27 (15)
Average number of daily patients		42.7±27.69	2-130 (40)
		n	**%**
Gender	Woman	83	94.3
	Man	5	5.7
Marital Status	Married	66	75.0
	Single	22	25.0
State of having children	Yes	65	73.9
	No	23	26.1
Educational Status	Vocational School of Health	7	8
	Two year degree	18	20.5
	Undergraduate	54	61.4
	Master	8	9.1
	Doctorate	1	1.1
Job description	Dialysis Nurse	73	83.0
	Dialysis Technician	15	17.0
Type of dialysis	Haemodialysis	68	77.3
	Peritoneal	20	22.7
The state of having a health professional spouse	Yes	17	19.3
	No	71	80.7
Presence of Chronic Disease	Yes	22	25.0
	No	66	75.0
The state of smoking	Yes	28	31.8
	No	60	68.2
The state of using psychiatric medication	Yes	7	8.0
	No	81	92.0

27.3% of the participants stated that they needed psychological counselling since the first COVID-19 case emerged; 59.1% stated that they felt more exhausted when compared with pre-COVID-19; 93.2% followed news about COVID-19; 53.4% stated that patients and their relatives did not take the situation seriously; 76.1% stated that they had sufficient information about COVID-19; 60.2% stated that the possibility of being infected with COVID-19 was higher when compared with other healthcare professionals (Table 2). It was found that 84.1% of the participants worried about infecting COVID-19 to their patients, 93,2% worried about infecting COVID-19 to their families, 89.8% worried about infecting COVID-19 to their colleagues and 34.1% worried about getting infected with COVID-19 themselves (Table 2). 86.4% of the healthcare professionals stated that they had sufficient information about how to protect from COVID-19, 64,8% stated that they were supplied with sufficient protective equipment for isolation, 47,7% stated that they felt psychologically safer when compared with healthcare professionals working in intensive care and infection clinics, 37.5% stated that they felt safer when compared with healthcare professionals working in intensive care and infection clinics in terms of being infected (Table 2).

Table 2. Information of the Participants about the COVID-19 Process

		n	%
Feeling the need to get psychological help since COVID-19 started	Yes	24	27.3
	No	49	55.7
	Undecided	15	17.0
Feeling more exhausted than pre COVID-19	Yes	52	59.1
	No	28	31.8
	Undecided	8	9.1
Following news with the first COVID-19 case	Yes	82	93.2
	No	4	4.5
	Undecided	2	2.3
Thinking that patients and their relatives are not taking the situation seriously	Yes	47	53.4
	No	23	26.1
	Undecided	18	20.5
Thinking that one has sufficient information about COVID-19	Yes	67	76.1
	No	6	6.8
	Undecided	15	17.0
Thinking that the risk of being infected with COVID-19 is higher than the other healthcare professionals	Yes	53	60.2
	No	19	21.6
	Undecided	16	18.2
Worrying about the possibility of infecting patients when infected with COVID-19	Yes	74	84.1
	No	10	11.4
	Undecided	4	4.5
Worrying about the possibility of infecting family when infected with COVID-19	Yes	82	93.2
	No	2	2.3
	Undecided	4	4.5
Worrying about the possibility of infecting colleagues when infected with COVID-19	Yes	79	89.8
	No	7	8.0
	Undecided	2	2.3
Worrying about being infected with COVID-19	Yes	30	34.1
	No	38	43.2
	Undecided	20	22.7
Having sufficient information about how to protect oneself	Yes	76	86.4
	No	2	2.3
	Undecided	10	11.4
Thinking that one does not have sufficient equipment to protect oneself	Yes	57	64.8
	No	16	18.2
	Undecided	15	17.0
Feeling psychologically safer than healthcare professionals working in intensive care and infection clinics	Yes	42	47.7
	No	22	25.0
	Undecided	24	27.3
Feeling safer than healthcare professionals working in intensive care and infection clinics in terms of this disease	Yes	33	37.5
	No	30	34.1
	Undecided	25	28.4

Table 3 includes data on level of information about COVID-19. 96.6% of the healthcare professionals answered the first question as correct, 27.3% answered the second question as incorrect, 83% answered the third question as correct, 36.4% answered the fourth question as incorrect, 100% answered the fifth question as correct, 59.1% answered the sixth question as correct, 75% answered the seventh question as incorrect, 62.5% answered the eighth question as incorrect and 95.5% answered the ninth question as incorrect (Table 3).

Table 3. Information levels about COVID-19

	Correct n(%)	**Incorrect n(%)**	**No Idea n(%)**
1. COVID-19 agent is a coronavirus.*	85 (%96.6)	0	3 (%3.4)
2.Coronavirus is not a virus family that causes disease in animals.*	58 (%65.9)	24 (%27.3)	6 (%6.8)
3.The coronavirus family is transmitted from animals to humans due to a mutation they develop.*	73 (%83.0)	7 (%8.0)	8 (%9.1)
4. The coronavirus family can be transmitted to pets though humans after they are transmitted from animals to humans.**	24 (%27.3)	32 (%36.4)	32 (%36.4)
5. The coronavirus family is transmitted from human to human through droplet*.	88 (%100.0)	0	0
6. COVID-19 virus is a different virus family than the agents of Sars and Mers epidemics.**	52 (%59.1)	26 (%29.5)	10 (%11.4)
7.The novel coronavirus group viruses become inanimate by applying salty water and vinegar to the nose. **	11 (%12.5)	66 (%75.0)	11 (%12.5)
8.The only organ affected by the novel coronavirus group viruses is the lung.**	28 (%31.8)	55 (%62.5)	5 (%5.7)
9. The novel coronavirus group viruses causes disease only in individuals who are older than 65 years of age and who have a comorbid disease**.	3 (%3.4)	84 (%95.5)	1 (%1.1)

*Correct answers, ** Incorrect answers

CAS total average score of healthcare professionals was found as 2.5±2.98 (Min-Max: 0-14. Median:2). High CAS scores of single participants (X:2.95±2.03), participants with a master degree (X:3.88±3.48) and those working in peritoneal dialysis unit (X: 3.05±2.42) were found to be statistically significant (Table 4;p<0.05).

Table 4. Comparison of participants' sociodemographic characteristics and average CAS scores

		CAS		
		Ave±ss	**Min-Max (Median)**	**p**
Gender	Woman	2.4±2.78	0-12 (2)	0.507
	Man	4.2±5.63	0-14 (3)	
Marital Status	Married	2.35±3.24	0-14 (1)	0.033*
	Single	2.95±2.03	0-7 (3)	
State of having children	Yes	2.48±3.23	0-14 (1)	0.347
	No	2.57±2.21	0-7 (3)	
Educational Status	Vocational School of Health	2.86±5.24	0-14 (0)	0.012*
	Two year degree	3.78±2.9	0-10 (3)	
	Undergraduate	1.87±2.41	0-10 (1)	
	Master	3.88±3.48	1-12 (3)	
Job description	Dialysis Nurse	2.42±3.18	0-14 (1)	0.079
	Dialysis Technician	2.87±1.81	0-6 (3)	
Type of dialysis	Haemodialysis	2.34±3.13	0-14 (1)	0.047*
	Peritoneal	3.05±2.42	0-8 (2)	
The state of having a health professional spouse	Yes	2.59±3.83	0-14 (1)	0.726
	No	2.48±2.78	0-12 (2)	
Presence of Chronic Disease	Yes	3±2.86	0-10 (3)	0.181
	No	2.33±3.02	0-14 (1)	
The state of smoking	Yes	2.68±3.35	0-12 (2)	0.916
	No	2.42±2.82	0-14 (1.5)	
The state of using psychiatric medication	Yes	4±4.47	0-10 (2)	0.625
	No	2.37±2.82	0-14 (2)	

Table 5 gives post-COVID 19 information of healthcare professionals and their CAS score averages. It was found that high CAS scores of participants who felt the need to get psychological help since the beginning of COVID-19 (X:4±3.86), those who felt more exhausted when compared with pre- COVID-19 (X: 3.58±3.36), those who thought their risk of being infected with COVID-19 was higher than other healthcare professionals (X:3.15±3.4) those who were undecided about worrying for themselves on being infected with COVID-19 (X: 3.4±2.66), those who had sufficient information about how to protect from COVID-19 (X:4.4±3.31) and those who stated that they were undecided about having been provided equipment (X:4.67±3.11) were statistically significant (Table 5; $p<0.05$).

Table 5. Comparison of participants post- COVID-19 information and CAS score averages

		CAS		
		Ave±sd	**Min-Max (Median)**	**p**
Feeling the need to get psychological help since COVID-19 started	Yes	4±3.86	0-14 (3)	0.008*
	No	1.71±2.47	0-12 (1)	
	Undecided	2.67±1.95	0-6 (3)	
Feeling more exhausted than pre COVID-19	Yes	3.58±3.36	0-14 (3)	0.001*
	No	0.86±1.15	0-5 (1)	
	Undecided	1.25±1.39	0-3 (1)	
Following news with the first COVID-19 case	Yes	2.56±3.06	0-14 (2)	0.810
	No	1.5±1.91	0-4 (1)	
	Undecided	2±1.41	1-3 (2)	
Thinking that patients and their relatives are not taking the situation seriously	Yes	2.64±2.67	0-10 (2)	0.462
	No	2.17±3.19	0-12 (1)	
	Undecided	2.56±3.58	0-14 (1)	
Thinking that one has sufficient information about COVID-19	Yes	2.28±3.1	0-14 (1)	0.084
	No	2.33±1.51	1-4 (2)	

	Undecided	3.53±2.77	0-10 (3)	
Thinking that the risk of being infected with COVID-19 is higher than the other healthcare professionals	Yes	3.15±3.4	0-14 (2)	0.032*
	No	1.16±1.61	0-5 (0)	
	Undecided	1.94±2.05	0-7 (1.5)	
Worrying about the possibility of infecting patients when infected with COVID-19	Yes	2.73±3.14	0-14 (2)	0.266
	No	1.3±1.49	0-4 (1)	
	Undecided	1.25±1.89	0-4 (0.5)	
Worrying about the possibility of infecting family when infected with COVID-19	Yes	2.63±3.04	0-14 (2)	0.159
	No	1±1.41	0-2 (1)	
	Undecided	0.5±1	0-2 (0)	
Worrying about the possibility of infecting colleagues when infected with COVID-19	Yes	2.68±3.06	0-14 (2)	0.118
	No	0.86±1.57	0-4 (0)	
	Undecided	1±1.41	0-2 (1)	
Worrying about being infected with COVID-19	Yes	3.13±3.92	0-14 (2)	0.013*
	No	1.53±1.87	0-7 (1)	
	Undecided	3.4±2.66	0-10 (3)	
Having sufficient information about how to protect oneself	Yes	2.32±2.89	0-14 (1)	0.016*
	No	0±0	0-0 (0)	
	Undecided	4.4±3.31	0-10 (3.5)	
Thinking that one does not have sufficient equipment to protect oneself	Yes	2.12±3.02	0-14 (1)	0.006*
	No	1.81±1.68	0-6 (1.5)	
	Undecided	4.67±3.11	0-10 (5)	
Feeling psychologically safer than healthcare professionals working in intensive care and infection clinics	Yes	2.55±3.28	0-14 (1)	0.304
	No	1.73±1.98	0-7 (1)	
	Undecided	3.13±3.15	0-10 (2.5)	
Feeling safer than healthcare professionals working in intensive care and infection clinics in terms of this disease	Yes	7.3±3.31	5-19 (6)	0.370
	No	7.2±2.46	5-15 (7)	
	Undecided	8.12±3.13	5-15 (7)	

3. DISCUSSION

The findings obtained as a result of the analysis of research data have been discussed in the light of related literature. It was found that 96.6% of the participants answered the question “COVID-19 agent is a coronavirus” correctly, while 65.9% answered the question “Coronavirus is not a virus family that causes disease in animals” correctly, 83% answered the question “The coronavirus family is transmitted from animals to humans due to a mutation they develop” correctly and 100% answered the question “The coronavirus family is transmitted from human to human through droplet” correctly. In addition, 75% of the participants answered the question “The novel coronavirus group viruses become inanimate by applying salty water and vinegar to the nose” as incorrect, 65.5% answered the question “The only organ affected by the novel coronavirus group viruses is the lung” as incorrect, 95.5% answered the question “The novel coronavirus group viruses causes disease only in individuals who are older than 65 years of age and who have a comorbid disease” as incorrect, 36.4% answered the question “The coronavirus family can be transmitted to pets through humans after they are transmitted from animals to humans” as incorrect and 29.5% answered the question “COVID-19 virus is a different virus family than the agent of Sars and Mers epidemics” as incorrect and thus gave the correct answer. Only in two questions (Question 4 and Question 6) the rate of correct answers was below 50%. In addition, 76.1% of the participants stated that they had sufficient information about COVID-19. According to

these results, it can be said that healthcare professionals had moderate level of information about COVID-19. Studies conducted have also reported that healthcare professionals have sufficient level of information about COVID-19 (Bhagavathula, Aldhaleei, Rahmani, Mahabadi, & Bandari, 2020; Huynh, Nguyen, Vo, & Pham, 2020; Nemati, Ebrahimi, & Nemati, 2020; Saqlain et al., 2020).

In the study, average CAS total score of the healthcare professionals was found as 2.5±2.98. According to this result, COVID-19 anxiety of healthcare professionals was found to be in moderate level. In their study, Du et al. (2020) found that healthcare professionals had high level of anxiety. In their study they conducted with healthcare professionals, Tan et al. (2020) found that anxiety level of healthcare professionals who provided medical care (doctors and nurses) was 2.45±4.28. In Lu et al.'s (2020) study conducted with healthcare professionals (doctors and nurses), anxiety level was found as 4.73±6.29. The fact that COVID-19 infection has a highly infectious potential and high mortality rates increases the anxiety level of healthcare professionals in the risk group.

In the study, the fact that single healthcare professionals had high CAS scores (X:2.95±2.03) was found to be statistically significant. During the pandemic, healthcare professionals prefer to stay away from their homes and family members for long periods of time and communicate with their loved ones without physical contact and usually on the phone. During this process, the obvious decrease in the emotional and

social support from the family and friends (Tuncay et al., 2020) has caused single healthcare professionals to experience higher anxiety.

High CAS scores of healthcare professionals who felt the need to get psychological support since COVID-19 started (X:4±3.86) and those who felt more exhausted than pre- COVID-19 (X: 3.58±3.36) were found to be statistically significant. Studies conducted have also reported that pandemic process causes fatigue and exhaustion in healthcare professionals, healthcare professionals are psychologically extremely sensitive and that this situation increases anxiety levels (Lai et al., 2020; Rana, Mukhtar, & Mukhtar, 2020; Jialin Wang et al., 2020). During the COVID-19 pandemic, continually increasing number of confirmed and suspected cases, overwhelming work load, depletion of personal protection equipment, lack of specific drugs and feelings of insufficient support can contribute to psychological and mental burden in healthcare professionals (Lai et al., 2020). Within the framework of measures taken in dialysis units due to the COVID-19 pandemic, the number of daily 2-3 sessions has been increased and the number of patients in each session has been decreased. This situation has increased the workload of healthcare professionals working in dialysis units. In addition, healthcare professionals provided care to COVID-19 diagnosed patients in isolation rooms prepared in the same centres. This situation wears the participants psychologically and can cause exhaustion.

High CAS scores of the participants who thought that the risk of being infected with COVID-19 was higher than the other healthcare professionals (X:3.15±3.4) and those who were undecided for themselves about being infected with COVID-19 (X: 3.4±2.66) were found to be statistically significant.

Safety is a primary concern in healthcare professionals. Seeing their colleagues intubated, losing the patients they provide care for, being afraid of infecting the disease to their families and loved ones can damage their feelings of safety. These problems have been reported especially in healthcare professionals working to fight SARS (Lee et al., 2005; P. Wu et al., 2009). These concerns may increase due to factors such as prolonged outbreak and uncertainties in the treatment. In a study in which the effects of SARS outbreak on 248 healthcare professionals working in Toronto (Canada) were examined, high psychological distress and anxiety symptoms were found in healthcare professionals. Although the variables that increase these factors are not fully explained, the effect of uncertainties in treatment protocols have been reported (Styra et al., 2008).

High CAS scores of the participants who stated that they had sufficient information about how to protect themselves against COVID-19 (X:4.4±3.31) and the participants who stated that they were undecided about not having sufficient equipment (X:4.67±3.11) were found to be statistically significant.

In line with the results of the present study, it was reported in a study conducted in Pakistan that high infection risk, isolation and insufficient security equipment increased the level of anxiety (Rana et al., 2020). The stressors that accompany the pandemic process have been reported as the fear of being infected, distress, insufficient personal protection equipment and insufficient information (Tuncay et al., 2020).

4. CONCLUSION

COVID-19 anxiety levels of the healthcare professionals (nurses and dialysis technicians) working in dialysis units were found to be in moderate levels. Feeling of exhaustion, the risk of being infected with COVID-19 and level of information about protection from COVID-19 affect healthcare professionals' level of anxiety. Considering that it is necessary to maintain mental health and that mental health plays an important role in strengthening immunity, administrators should take the necessary measures to decrease anxiety levels of healthcare professionals. It is also recommended to give the necessary trainings on strategies to deal with anxiety.

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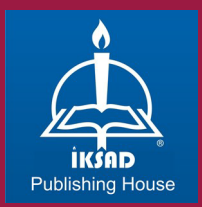

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