European Journal of Biomedical and Life Sciences

№ 1 2022

PREMIER
Publishing

Vienna
2022

European Journal of Biomedical and Life Sciences

Scientific journal

№ 1 2022

ISSN 2310-5674

Proofreading Kristin Theissen
Cover design Andreas Vogel
Additional design Stephan Friedman
Editorial office Premier Publishing s.r.o.
Praha 8 – Karlín, Lyčkovo nám. 508/7, PSČ 18600
E-mail: pub@ppublishing.org
Homepage: ppublishing.org

European Journal of Biomedical and Life Sciences is an international, German/English/Russian language, peer-reviewed journal. It is published bimonthly with circulation of 1000 copies.

The decisive criterion for accepting a manuscript for publication is scientific quality. All research articles published in this journal have undergone a rigorous peer review. Based on initial screening by the editors, each paper is anonymized and reviewed by at least two anonymous referees. Recommending the articles for publishing, the reviewers confirm that in their opinion the submitted article contains important or new scientific results.

Premier Publishing s.r.o. is not responsible for the stylistic content of the article. The responsibility for the stylistic content lies on an author of an article.

Instructions for authors

Full instructions for manuscript preparation and submission can be found through the Premier Publishing s.r.o. home page at: http://www. ppublishing.org.

Material disclaimer

The opinions expressed in the conference proceedings do not necessarily reflect those of the Premier Publishing s.r.o., the editor, the editorial board, or the organization to which the authors are affiliated.

Premier Publishing s.r.o. is not responsible for the stylistic content of the article. The responsibility for the stylistic content lies on an author of an article.

Included to the open access repositories:

ULRICHSWEB GLOBAL SERIALS DIRECTORY · НАУЧНАЯ ЭЛЕКТРОННАЯ БИБЛИОТЕКА eLIBRARY.RU · CYBERLENINKA · Google scholar

GIF GLOBAL IMPACT FACTOR The journal has the GIF impact factor .562 for 2018.

Typeset in Berling by Ziegler Buchdruckerei, Linz, Austria.
Printed by Premier Publishing s.r.o., Vienna, Austria on acid-free paper.

Section 1. Life Sciences

https://doi.org/10.29013/ELBLS-22-1-3-13

Wenqiao Yu,
School: St. Andrew' DE
United State of America
E-mail: danny.yu331@gmail.com

DYSREGULATION OF ALTERNATIVE SPLICING IS INVOLVED IN MAJOR DEPRESSIVE DISORDER

Abstract. Major Depressive Disorder (MDD) is a mental disorder caused by brain malfunction. It's one of the most common mental disorder, effecting over 7% of the population. Most studies agree that MDD is most likely caused by many different factors, some genetic and some environmental, instead of one specific single nucleotide polymorphism (SNP). This study collected numerous SNPs related to MDD and looked at the function of these genes. We selected the most significant one, alternative splicing for further analysis. By taking a closer look at the three genes that are directly involved in alternative splicing, which are CELF4, RSRC1, and RBFOX1, we were able to understand how it effect the brain. The gene RSRC1 increased the gene expression in the brain and nerves. Data from other studies also showed that CELF4 and RBFOX1 and decrease the gene expression level in other organs. To sum those data up, the dysregulation of alternative splicing can cause the gene expression in different organs to alter in a way that increase the risk of MDD. The systematic abnormity of the alternative splicing process plays an essential role in MDD. Using this study, scientist will be able to better understand how alternative splicing can contribute to MDD and some genes associated with this process.

Keywords: Major Depressive Disorder, single nucleotide polymorphism, SNP, alternative splicing, gene expression level.

Introduction to Major Depressive Disorder

Major Depressive Disorder (MDD) is a serious medical and mental illness caused by brain malfunction. Life experiences, especially chronic pressure and physical/sexual abuse, can trigger brain malfunction, ultimately causing depression. Stress can cause epigenetic marks on the DNA and the chromatins. These marks can toggle genes in a way that trigger depression [5]. The exact neutral basis for depression is still unclear. Possible proposals for the cause include short gene alleles or the chromosome 3p25–26 [20]. However, studies have showed that a depressed brain has some important differences including grey matter abnormalities, brain shrinkage, and a more active amygdala [3].

Because it is a mental disorder, there are few to no external signs of depression. However, depression is more than sadness, also grief is one of the symptoms. Furthermore, other important symptoms include loss of interest in daily activities for a stretch

of time, feelings of worthlessness and self-loathing, and hopelessness. Not only does MDD effect one's emotion, but it can also have effect on the victim's physical appearance as depression can cause its victim to loss appetite [21].

Many studies have confirmed that depression is heritable by about 40 to 50 percent, which meant that about half the cause for MDD is genetic while the other half is due to life experiences. It has been suggested that there is no definite way to avoid MDD, as some may get it without experiencing drawback or pressure in life, whoever studies have demonstrated that the heritability of MDD caused the offspring of those with depression is more likely to get it. Someone with a family member suffering from depression has a 2- or 3-times greater risk, while those with a parent or sibling with recurring depression have a 4 to 5 times greater risk [1].

As previously stated, the exact genetic cause of MDD is unclear, however most studies agree that MDD is unlikely caused by a single gene. On the contrary, it's more likely caused by a combination of change of amino acid in single nucleotide polymorphism (SNP) that are related to MDD. Those SNPs and genes work collectively to affect the brain and the neurons which lead to MDD.

This study performed an analysis of the SNPs that are related to MDD. A total of 440 SNPs, which represent 145 different genes, are collected and analysis to determine their functions and how they contribute to the cause of depression. Then the study focused on one important function that is affected by these genes and looked closely at the genes that directly effect this function. The expression level of these is then measured and compared to other depression cases. Lastly this study looked at the relationship between the numerous genes that are believed to contribute to MDD.

Material and Method

SNP Collection

First, in order to gather SNPs that are associated with MDD, the tool GWAS Central (Genome-Wide Association Study) (https://www.gwascentral.org) was used. Using the search bar under "Phenotypes", depression was searched. Multiple studies with a high amount of "Total p-value in study" were located. All of these SNPs have a OR value that is bigger than 1, which meant that the occurrence of this SNP will increase the chance of depression. The OR value is the ration between two conditions (control and depression. All of the SNP chosen also have small p-values. P-value is the number that indicate whether the result is likely caused by chance. A p-value of less that 0.05 meant that the result is significant and reliable, unlikely due to chance. Most, if not all of the SNPs chosen for this study have a p-value that is less than 0.05, which strengthened the link between the case of depression and the individual SNP markers.

SNP Annotation

The tool wANNOVAR (https://wannovar.wglab.org/), a website that functionally annotate genetic variants, was used to annotate all 440 of the SNPs. wANNOVAR yielded information such as which chromosome the SNPs are on, which SNP is an exon, and the Official Gene Symbol for each SNP.

Enrichment Analysis

Thirdly, DAVID (https://david-d.ncifcrf.gov/) was used for functional enrichment analysis. It was used to better understand the major function of these genes. It also serves to provide the Gene Ontology terms to help understand the biological meaning of each gene. This website also provided links that are helpful in learning about each function effected by the genes.

Gene Information

Then, SOURCE search (https://source-search.princeton.edu/) was used to find the genes that directly affect the alternative splicing process. By enter all of the Official Genes Symbols into the website and then searching for "splic".

Then NCBI (www.ncbi.nlm.nih.gov) and DAVID was used again to get a deeper understanding for each of these genes. NCBI is an extreme helpful source as it has numerous sources for different pur-

poses. It is a website that was utilized a lot later in this study. Then the document that is annotated by wANNOVAR was used to identify the specific SNPs in each gene.

To better understand the structure of each gene and the position of the SNPs on each gene, the UCSC Genome Browser (https://genome.ucsc.edu/cgi-bin/hgGateway) was utilized. This website provides a tool that display the position of each gene on the chromosome and which exon or intron each SNP sit on.

Expression Level Analysis

After that, specific SNP was studied for their potential effects on gene expression using GTex Portal (https://gtexportal.org/home/). This website showed whether a specific SNP will cause the expression level in certain areas to increase or decrease. Because the illness studied is depression, this study focused on the expression level change in the brain and nerves. All of the variation in expression level has a low p-value to ensure that they will have potential effect on the cause of depression.

Then, NCBI was utilized again to search for other studies that contain the expression level of patients with MDD and the control. By analyzing with GEO2R, the average expression level was collected. In addition to calculating the average, a student's t-test was performed on each comparison set to get the p-value. Several comparison cases have a low p-value, ensuring that the difference between the control and MDD cases was not caused by chance.

Network Analysis

Lastly, STRING (https://string-db.org/) was used in attempt to find connections between all of the genes that contribute to depression. This tool gave a clear diagram displaying the relation of each gene related to depression on a web.

Results

Data and Statistics

In the study, first the data from GWAS Central database was used to identify SNPs that are associated with the occurrence of MDD. We found 9 different studies with a high amount of "total p-value in study". These 9 studies contain a total of 440 SNPs. All of these SNPs have an OR value that is bigger than one, which means that they all have a positive relationship with the occurrence of MDD. Then the list of SNPs was into a vcf file and submitted that to wANNOVAR. Out of the 440 SNPs collect, only one is exonic. This SNP belong to the gene DENND1B (DENN domain containing 1B). This gene functions as guanine nucleotide exchange factors (GEFs) for the early endosomal small GTPase RAB35 and bind to clathrin as well as clathrin adaptor protein-2.

These SNPs account for a total of 140 different genes. Some genes show up multiple times and have multiple SNPs. Below is a table of all the genes that show up repeatedly for 5 or more times.

Table 1.– MDD related genes that repeatedly show up and their SNPs

GENE	SNPs
DCC	rs149735550; rs62097899; rs11663393; rs4277413; rs7505145; rs8084351; rs7227069; rs4632195; rs12968428; rs8099160; rs62100776; rs1431181; rs8089865
RBFOX1	rs8063603; rs7193263; rs7198928; rs7198928; rs3785234; rs2191130; rs2191130;
SORCS3	rs61867293; rs1021363; rs2496022; rs1961639; rs7074335
CNTN5	rs1690818; rs1690816; rs2458167; rs586533
GRM5	rs1150313; rs7932640; rs7126679; rs10741299; rs10830220
S0X5	rs4074723; rs78337797; rs17487383
TCF4	rs1262465; rs1261070; rs12967143; rs12958048; rs1452788; rs4801157

Showing up repeatedly meant that these genes are included in many studies. Being found in many studies proved their significance and connection to MDD.

Alternative Splicing is One of the Most Important Function

Then we investigated the main function effected by these genes with DAVID. Using DAVID's functional annotation tool, we were able to get the enrichment annotation for these genes. The main effects of these genes include alternative splicing and changes to phosphoprotein, dendrite, and cell junction.

Table 2. – Top 10 Terms from DAVID's Functional Annotation Chart and their corresponding statistic. Gene Count is the number of gene involved in this term and% of genes involved is the ratio between the gene count and the total amount of genes entered

Terms	Gene Count	% of genes involved	P-value
splice variant	78	55.7	1.30E–08
Alternative splicing	88	62.9	9.80E–06
Membrane	68	48.6	3.20E–05
Phosphoprotein	70	50.0	2.30E–04
Dendrite	10	7.1	3.10E–04
Learning	5	3.6	4.90E–04
Cell Junction	13	9.3	7.30E–04
Synapse	9	6.4	1.40E–03
dendrite morphogenesis	4	2.9	1.70E–03
Guanine-nucleotide releasing factor	6	4.3	2.00E–03

Out of every term, alternative splicing involves the most genes out of the list in this study, while it also has the lowest p-value. Alternative Splicing is a process during gene expression that allows a single gene to code for multiple proteins, thus allowing for gene diversity. The statistics in (table 2) meant that a lot of genes go through the alternative splicing process and is significantly affected by it. Alternative splicing is significantly enriched by these genes and its likely to effect MDD. Therefore, this study is going to focus on genes associated from alternative splicing from this point on.

Three Genes are Directly Involved in Alternative Splicing

In order to find the genes that are directly involved in the process of alternative splicing, SOURCE search developed by Princeton University was used. By entering the official gene symbols, we receive the function and classification of each gene. We found that three genes are directly involved in the process of alternative splicing. Those genes are CELF4 (CUGBP, Elav-like family member 4), RSRC1(arginine and serine rich coiled-coil 1), and RBFOX1(RNA binding protein, fox-1 homolog 1). In addition to being directly involved in alternative splicing, these 3 genes also go through the process themselves.

In order to learn more about each gene, the database on NCBI was utilized. Meanwhile the links on DAVID are also helpful in enhancing my understanding of these genes.

CELF4, also known as BRUNOL4, is a member of the CELF/BRUNOL protein family. This protein family is mainly responsible for regulating pre-mRNA alternative splicing. It can also take part in in mRNA editing and translation. More specifically, CELF4 regulates translation and local abundance of numerous mRNAs, including those associated with regulation of synaptic function. This gene can cause a biased expression in brain and adrenal [17].

RSRC1 encodes for a member of the serine and arginine-rich related protein family. It's involved in both the constitutive and alternative mRNA splicing process, which can lead to multiple transcript variants encoding different isoforms. This gene might be associated with schizophrenia and has been implicated in various neurological disorders [18].

RBFOX1 belong to the FOX-1 family of RNA-binding proteins. It's an RNA-binding protein that regulates alternative splicing events through binding with 5'-UGCAUGU-3' elements. RBFOX1 isoforms specifically activate splicing of neuronally regulated exons, which requires UGCAUG enhancer elements. This gene may cause biased expression in the brain or heart [19].

Table 3. – Information on the 3 genes that are directly involved in alternative splicing. Corresponding SNPs are listed in the last column

Symbol	Name	GeneID	Cytoband	SP Local	UniProt	SNP
CELF4	CUGBP, Elav-like family member 4	56853	18q12	nucleus	Q9BZC1	rs4799936; rs1557341; rs12967855; rs11082011; rs11665070
RSRC1	arginine/serine-rich coiled-coil 1	51319	3q25.32	nucleus	Q96IZ7	rs6441175; rs1095626; rs7430565
RBFOX1	RNA binding protein, fox-1 homolog (C. elegans) 1	54715	16p13.3	nucleus	Q9NWB1 B7Z1U7 Q59HD3	rs8063603; rs7193263; rs7198928; rs7198928; rs3785234; rs2191130; rs2191130

Each of these genes include multiple SNPs from the initial data of all 440 SNPs. Each of them contains at least 3 or more SNPs, meaning that multiple studies have also identified these genes.

All of the MDD related SNPs are Located in Non-exon Regions

To better understand the structure of the genes where these SNPs sit on, and each individual SNPs specific position on the gene, the UCSC Genome Browser was used as it clearly displayed the position of each gene. All of the SNPs are intronic, however they are still important as they can have effect on gene expressions and importantly impact the gene. The figure below indicates the specific location of each SNP on their gene.

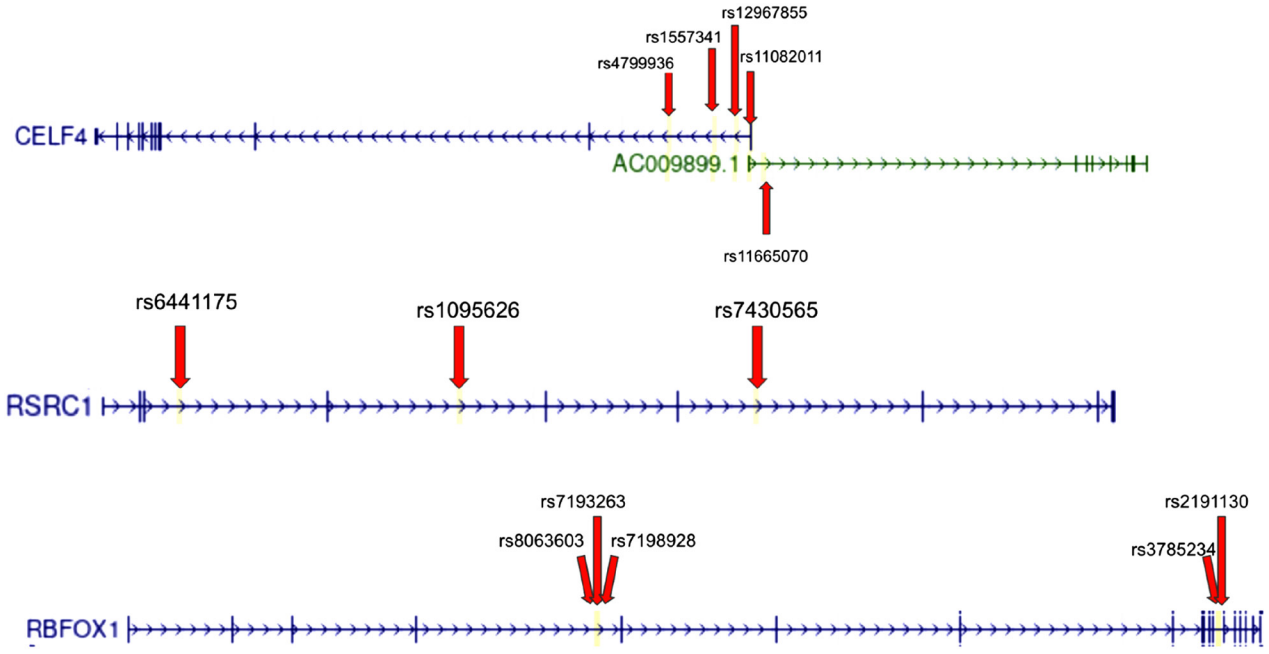


Figure 1. CELF4, RSRC1, and RBFOX1 gene structure and SNP position

On the horizontal blue line that symbolize a gene, each blue vertical dash represents one exon while the part between each exon are introns. Because all of the red arrows, which points to the position of a SNP in the gene, are located between the vertical dashes, they are all intronic. The arrows on each gene represent the direction of the gene and whether it's up or down stream. If the arrow is pointing to the left, then the gene is downstream. If the arrow is to the right, then the gene is upstream.

Alternative Splicing Associated Genes Increase Expression Level in the Brain and Nerves

These SNPS and their variations can change the expression level of genes. To figure out the potential expression level change, we used GTex Portal to search for each SNP. The table below indicate the potential change in expression level caused by these SNPs. Although all of the SNPs listed in the above table are search, only two yielded reliable result (rs1095626 and rs7430565). Both SNP is a part of the gene RSRC1. It doesn't mean the other SNPs have no effect; however, they need to be further investigated. The first two figures on the top come from the SNP rs1095626. The risk allele for this SNP is C, which is displayed to the right of each figure. Therefore, the gene expression goes from control on the left to SNP case to the right. In the bottom two figure, which come from the SNP rs7430565, the risk allele is G. Because G is to the left of the two figures in the bottom, the figure goes from controlled to the right to SNP to the left. In all four variations, the gene expression amount has been increased. It's also worth noting that all of these variations have a low p-value, making them significant and not by chance.

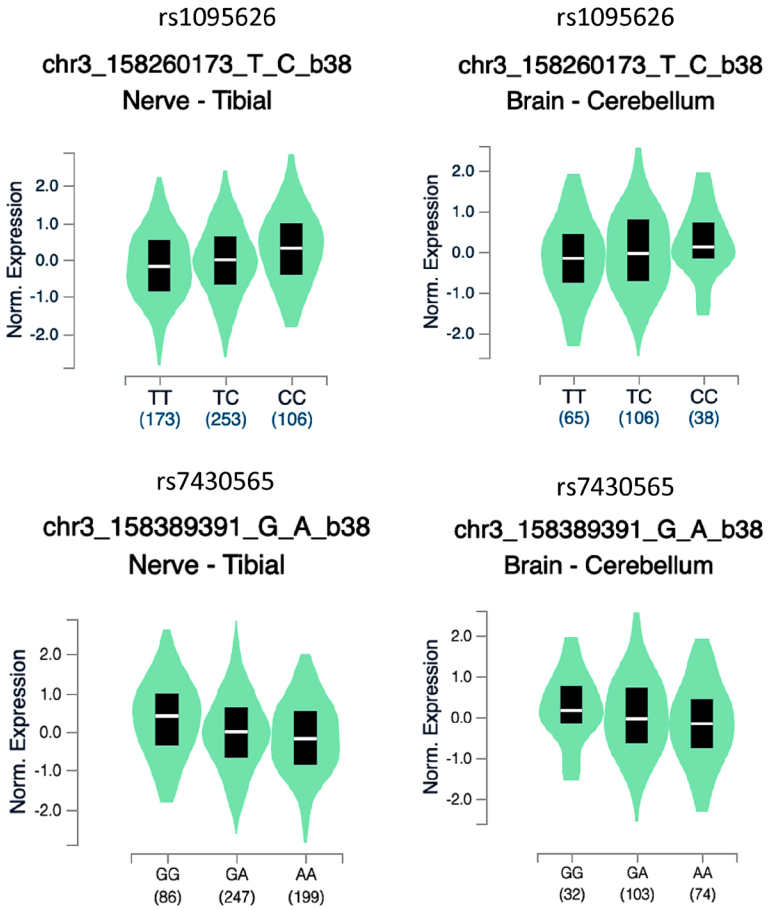


Figure 2. MDD associated genetic variations' effect on gene expression. All graphs come from either variation in the brain or nerves. All variations come from the gene RSRC1

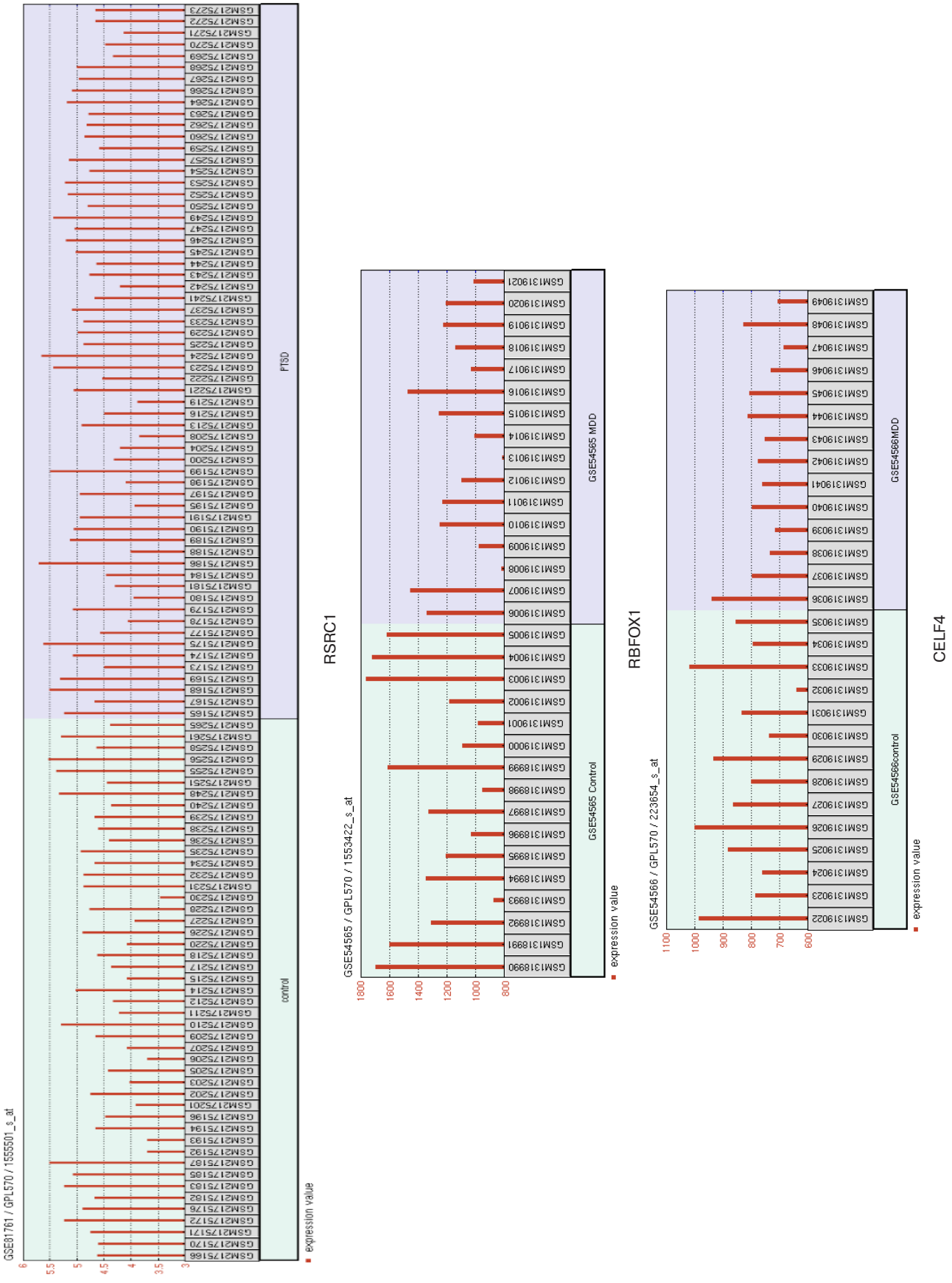


Figure 3. Diagrams of most change in gene expression level for each gene

As the graph has shown, the gene expression level has been increased, causing its original function to be enhanced.

CELF4, RSRC1, and RBFOX1 are Dys-regulated in Gene Expression in MDD

In order to understand how the gene expression level are different in MDD patients and the control, NCBI was used again to search for different studies. There are a total of 8 studies that provide a comparison between the expression level of controlled cases and MDD cases. It's worth noting that not all of these studies focused on the same aspect as this study, for example one of them provided data for blood sample, however they still provided information on whether gene expression level change will contribute to depression. After sorting the data from each study into controlled versus MDD, we searched the IDs for each gene. Each of these three genes can have multiple different Probe Set IDs, and each can have different expression level.

The GEO2R analysis function in NCBI provided a diagram that compares the expression level of both MDD cases and controlled cases. Out of all the studies, there were 13 cases where the expression level is visibly different. Then took the sample data and used the AVERAGE and TTEST function to find the average and p-value for each set of comparison. There are a total of 4 cases where the MDD cases' expression level is slightly higher, while there are 9 cases where controlled have a higher expression level. In all of the 13 cases, 8 cases have a low enough p-value to be considered significant. In those 8 cases, 7 cases showed that the controlled case has a higher expression level. In all of the diagrams, the left (green) represents the expression level from controlled cases, while the right (purple) represents the expression level from MDD cases.

Table 4. – Gene expression level comparison from different studies. The GEO accession is the code for each study that can allow for easy navigation in NCBI. The Expression Level Change shows whether the gene expression level increased or decreased from controlled to MDD

GENE	GEO accession	Probe Set ID	Expression Level Change	p-value
RSRC1	GSE81761	1555501_s_at	increase	0.036166143
RBFOX1	GSE81761	1553422_s_at	decrease	0.033248424
RBFOX1	GSE81761	235070_at	decrease	0.056357117
RBFOX1	GSE54565	1553422_s_at	decrease	0.046421725
CELF4	GSE81761	231220_at	decrease	0.051945508
CELF4	GSE81761	232719_at	decrease	0.026451222
CELF4	GSE54568	223653_x_at	decrease	0.061491506
CELF4	GSE54566	223654_s_at	decrease	0.034136362

As shown in the table above, most studies showed a decrease in gene expression for the MDD cases while still keeping the p-value relatively low. It's worth noting that although the trend shows a decrease of expression level, the genes expression level for RSRC1 (first row in table 4) increased. This stayed consistent with the data in (figure 2), where both SNPs showed an increase in gene expression in the brain and nerves.

In addition to the table, below are three graphs, one for each gene, that represent the most change in gene expression.

In the above figures, the letter to the left of each diagram correspond to the label in (table 7). For each figure, each red bar represents the expression level for one case. The controlled cases are always to the left in the green section while the MDD cases are always to the right in the purple section.

In conclusion to the data gather, these genes can cause systematic abnormality in the alternative splicing process. This can lead to an altar of expression level in many places and organs. As (table 5) states, the gene RSRC1 increased the expression level in the brain and nerves, enhancing the function of this gene. In other organs, such as blood or different part of the brain, the expression level was decreased, as stated in (table 10).

Network Analysis Reveals Interaction Among MDD-associated Genes

In order to further understand the relationship between all of the genes involved, STRING as used to produce a network of all the genes identified at the beginning of the study. Many of the genes that might contribute to MDD have some level of connection between them, while there are also a decent number of genes isolated from the overall network.

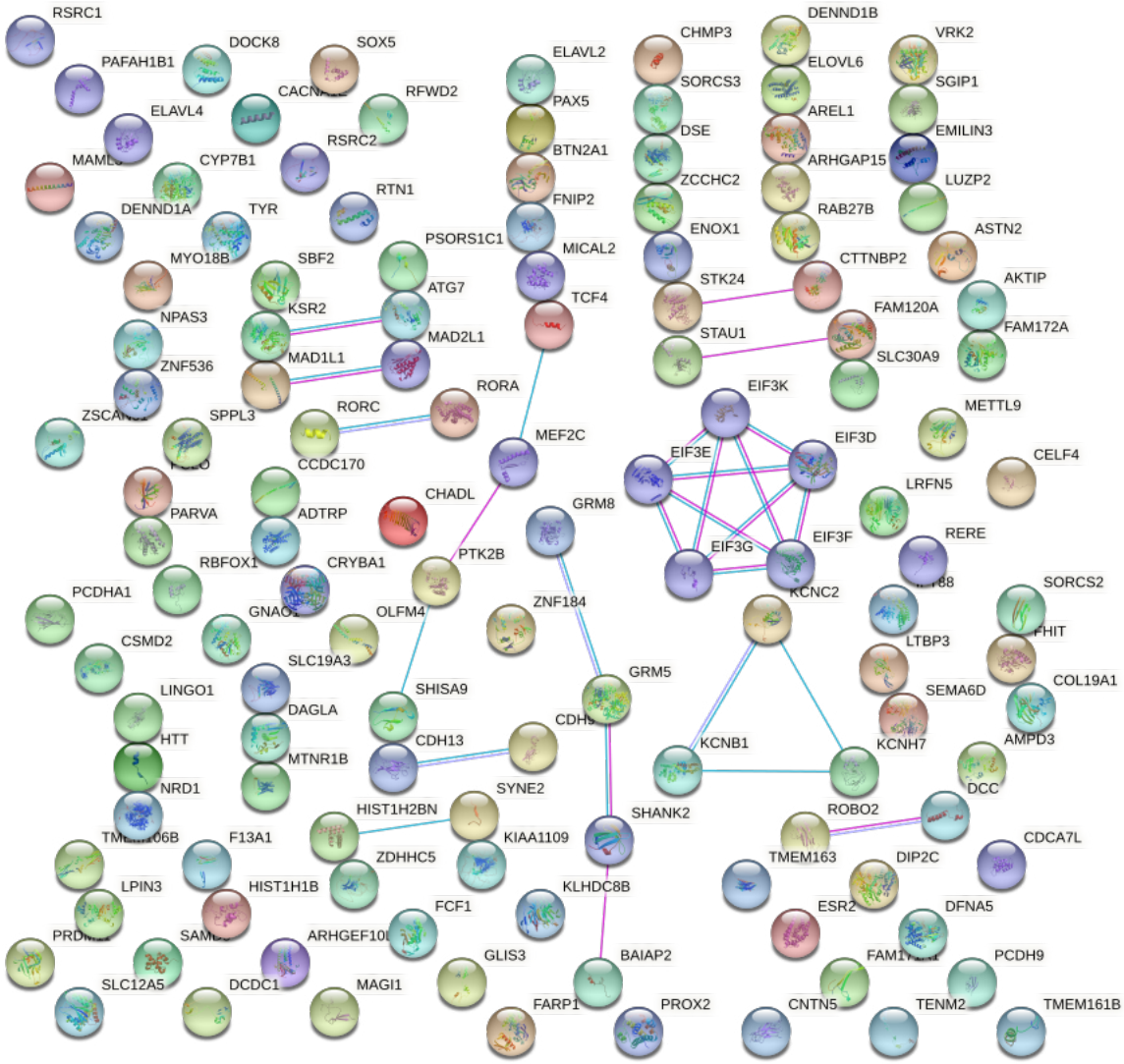


Figure 4. MDD related Gene Connection Network

In the above diagram, blue lines connecting two genes represent known interactions from curated databases and pink lines between two genes represent experimentally determined interactions.

A large portion of these genes don't have known interactions with each other, including the three genes this study primarily focused on. Most of the

genes are not in one network, rather, effecting a wide variety of genes and organs.

There are a few clusters of genes with known interaction with each other. The most notable interactions happened between the EIFs family. These genes include EIF3E, EIF3K, EIF3D, EIF3F, and EIF3G. All of these 5 genes have both known interactions from databases and experiments. Some other examples are the connection between GRM8, ZNF184, GRM5, SHANK2, and BAIAP2, and the connection between KCNC2, KCNB1, and KCH7.

Discussion

Alternative splicing happens with a unique pattern in the human brain and controls multiple aspects of early neuronal development. The diversity of these splicing patterns dictate important regulatory decisions in many stages of neuronal development. In mature neurons, synaptic remodeling and strengthening are all regulated by alternative splicing and the relative expression levels of Amplicon sequence variant. The splicing events that control neuronal activity are regulated by incoming stimuli, for example chronic excitatory depolarization [14].

The precursor-mRNA splicing reaction is essential in the regulation of gene expressions. Most genes produce multiple mRNA isoforms through such process to produce proteins with different structures and functions. In addition, the nervous system makes use of splicing regulation to produce specialized protein isoforms that will importantly affect many aspects of neuronal development [15].

The alternative splicing process is regulated by specialized pre-mRNA binding proteins that alter spliceosome assembly. Some of these regulators show tissue-specific expression, whereas others show more universal expression level, however they all regulate large overlapping programs of neuronal alternative splicing events. This support the why the gene expression level increased in the brain and nerves, as shown in figure 5, however showed a decreasing trend in other studies that are surveyed later [15].

The serotonin-1A (5-HT1A) receptor is crucially in regulating serotonergic activity and is implicated to have emotional effect. When the human HTR1A RNA is alternately spliced, this splicing removes a microRNA site increase HTR1A expression. This splicing can varies in different brain regions but is generally reduced in MDD. Un-spliced HTR1A was also shows stronger expression in the hippocampus and midbrain in comparison to the prefrontal cortex. This could explain why the systematic abnormality in alternative splicing can decrease the expression level in many of the studies that we surveyed [6].

References:

1. Douglas F. Levinson M. D., Walter E. Nichols M. D. Major Depression and Genetics.n.d.
2. Felix Torres M. D. What Is Depression. October, 2020.
3. Alyssa. Depressed Brain vs. Normal Brain. 24 Mar. 2021.
4. Nancy Schimelpfening. How Genetics Can Play a Role in Depression. December 03, 2020.
5. Eric J. Nestler. The Genetics of Depression: What is Known, What is Next. November 2017. Video available from: URL: https://www.hopefordepression.org/research-funding-and-impact/video-genetics-depression
6. Le François B., Zhang L., Mahajan G. J., Stockmeier C. A., Friedman E., Albert P. R. A novel alternative splicing mechanism that enhances human 5-HT1A receptor RNA stability is altered in major depression. J Neurosci. 2018; 38: 8200–10. 10.1523/JNEUROSCI.0902-18.2018
7. Chang L. C., Jamain S., Lin C. W., Rujescu D. et al. A conserved BDNF, glutamate- and GABA enriched gene module related to human depression identified by coexpression meta-analysis and DNA variant genome-wide association studies. PLoS One 2014; 9(3): e90980. PMID: 24608543

8. Rusch H. L., Robinson J., Yun S., Osier N. D. et al. Gene expression differences in PTSD are uniquely related to the intrusion symptom cluster: A transcriptome-wide analysis in military service members. Brain Behav Immun 2019. Aug; 80: 904–908. PMID: 31039430
9. Leday G. G.R., Vértes P. E., Richardson S., Greene J. R. et al. Replicable and Coupled Changes in Innate and Adaptive Immune Gene Expression in Two Case-Control Studies of Blood Microarrays in Major Depressive Disorder. Biol Psychiatry, 2018. Jan 1; 83(1): 70–80. PMID: 28688579
10. Sibille E. Molecular Evidence for a Dimensional Basis of Depression. Jan 01, 2016.
11. Chang L. C., Jamain S., Lin C. W., Rujescu D. et al. A conserved BDNF, glutamate- and GABA-enriched gene module related to human depression identified by coexpression meta-analysis and DNA variant genome-wide association studies. PLoS One 2014; 9(3): e90980. PMID: 24608543
12. Lanz T. A., Reinhart V., Sheehan M. J., Rizzo S. J. S. et al. Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. Transl Psychiatry, 2019. May 23; 9(1): 151. PMID: 31123247
13. Kong S. W., Collins C. D., Shimizu-Motohashi Y., Holm I. A. et al. Characteristics and predictive value of blood transcriptome signature in males with autism spectrum disorders. PLoS One 2012; 7(12): e49475. PMID: 23227143
14. Glatt S. J., Cohen O. S., Faraone S. V., Tsuang M. T. Dysfunctional gene splicing as a potential contributor to neuropsychiatric disorders. Am. J. Med. Genet. Part B: Neuropsychiatric Genet. 2011; 156:382–392.
15. Vuong C. K., Black D. L., Zheng S. The neurogenetics of alternative splicing. Nat. Rev. Neurosci. 2016; 17: 265–281. Doi: 10.1038/nrn.2016.27.
16. Pandya M., Altinay M., Malone D. A., Anand A. Where in the Brain Is Depression? Curr. Psychiatry Rep. 2012; 14: 634–642. Doi: 10.1007/s11920–012–0322–7.
17. [Gene [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004 – [cited 2021, Aug, 31]. Available from: URL: https://www.ncbi.nlm.nih.gov/gene/56853
18. Gene [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004 – [cited 2021, Aug, 31]. Available from: URL: https://www.ncbi.nlm.nih.gov/gene/51319
19. Gene [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004 – [cited 2021, Aug, 31]. Available from: URL: https://www.ncbi.nlm.nih.gov/gene/54715
20. Stephanie Faris. Is Depression Genetic? April 5, 2021.
21. The American College of Obstetricians and Gynecologists. Depression. June 2005. Available from: URL: https://dmh.lacounty.gov/our-services/employment-education/education/depression

https://doi.org/10.29013/ELBLS-22-1-14-19

Peiran Zhang,
Miss Hall's School, Pittsfield, MA
E-mail: peiran.zhang@misshalls.org

AN INVESTIGATION OF THE CAUSES BEHIND LONGEVITY

Abstract. Life expectancy around the globe is a significant indicator for living conditions, economic development, healthcare system, and equality in society. The data used in this research includes information on life expectancy among 223 countries and different genders. By comparing the disparity between regions and genders, along with other resources, we can investigate the impact of different aspects on people's lives. These aspects include prosperity, the healthcare system, and living style. It has been found that several biological and psychological factors – including social expectations, influences of masculinity and femininity, and living and working conditions – might contribute to the differences between genders. The goal of the analysis is to reveal the causes behind the difference in people's longevity. These causes are hopefully thought-provoking and can help people and governments make decisions in different areas.

Keywords: life-expectancy, health, gender, country.

Introduction

As humans, life expectancy is an important indicator of living standards, medical advancement, access to education, economic security, and government effectiveness. Due to various external factors, however, the expected length of life could vary depending on our living regions or genders.

The dataset used in this research is from the world health organization in 2019. It contains 6 columns and 223 Rows. Each row represents a country with their life expectancy rank. Out of the 6 columns, 4 have the numeric data-type. They are "Rank", "Overall Life Expectancy", "Male Life Expectancy" and "Female Life Expectancy". The two object-type columns are "Country" and "Continent" which shows where the country is located. The male and female life expectancies are shown separately for each country which poses interesting questions for analysis. The data include 223 unique values in the "Country" column which includes several non-sovereign entities. The countries correspond to six continents that are "Europe", "Asia", "Oceania", "North America", "Africa", and "South America".

While analyzing the differences, it's been found out that there are factors that might play an important role here. Intriguing what actually causes the differences between life expectancy, with the use of data analysis, the real cause of this discrepancy in life expectancy and the intersections of factors that might have affected the results have been further investigated.

Analysis

Since the life expectancy data vary due to countries and genders, in order to better analyze the data, different plots were made to visualize different countries and genders. With the data collected and the results shown by graphs, the analysis will help explain what various psychological factors might contribute to the differences.

The (Figure 1) below shows the histogram of "Overall life expectancy", "female life", "male life", and "Continent". They illustrate the distribution of data in these four columns. Female life expectancies, peaking around 80, are 5–10 years longer than their counterparts, in general. Europe, Asia, and Africa have the most data due to their population size.

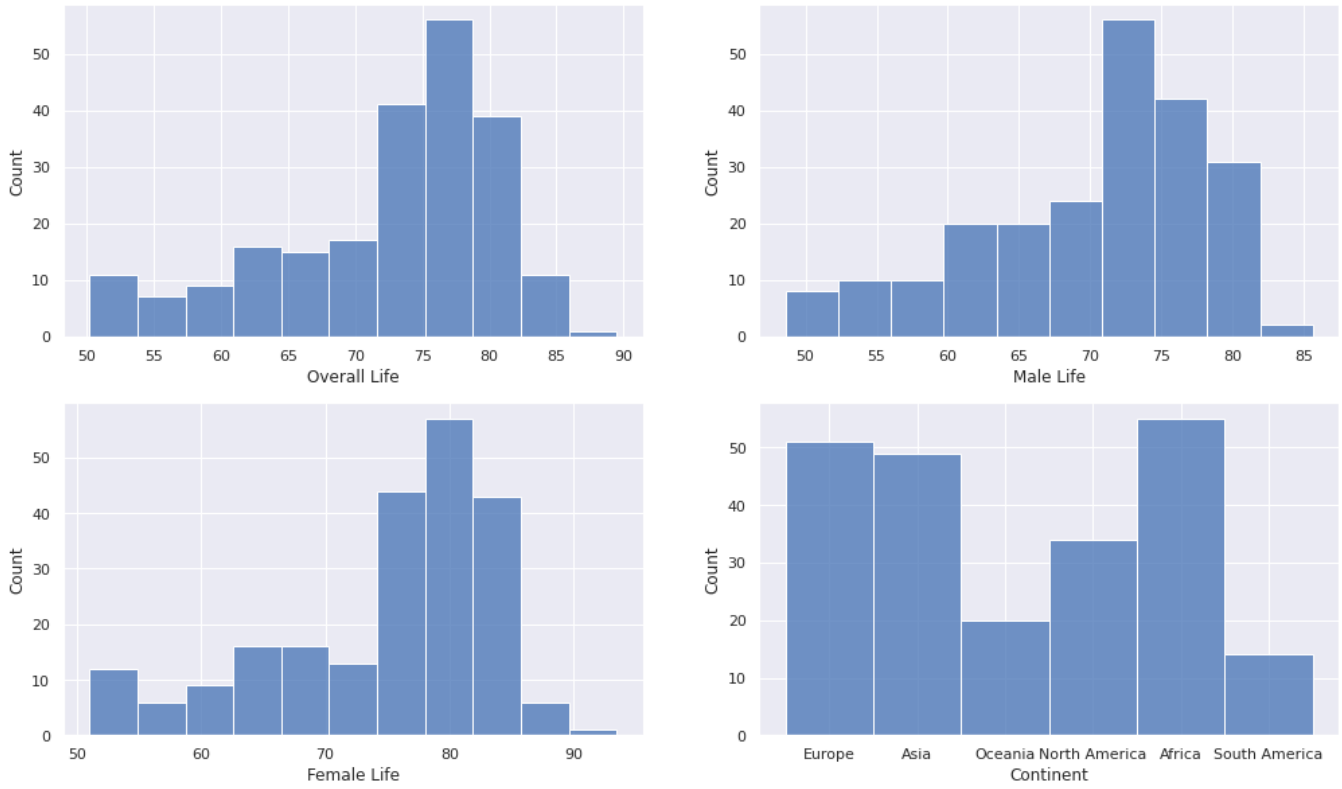


Figure 1. Histogram of every feature column in the dataset

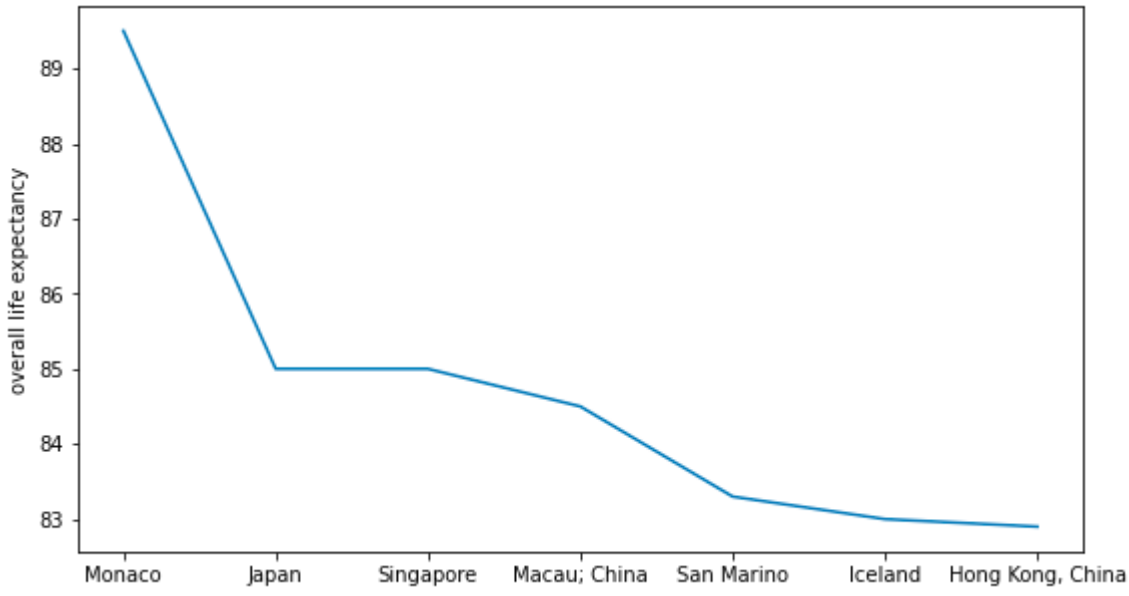


Figure 2. Overall Life-expectancy

As (Figure 2) shown above, people residing in different countries have different life expectancies, and the Top 5 are Monaco, Japan, Singapore, Macau(China), and San Marino, ranging from 89.5 to 83.3. According to the research, the differences of life expectancy among countries could simply be attributed to the differences in diet, public health, and healthcare services. For instance, the sanitation conditions include the access to clean drinking water which is crucial for one's living condition;

the medical services allow its citizens to receive appropriate medical treatments, and the healthy eating habits contribute to the wellness of people. In Monaco, for instance, people have an overall life expectancy around 89.5, the longest in the world. Monaco is located along the Mediterranean Sea, with its economic prosperity and a temperate climate, people there have access to the healthiest diet – seafood, fruit, and vegetables, which thus leads to the rise of life-expectancy. Monaco also offers an excellent healthcare system. Another example is Japan, whose overall life-expectancy is 85, the second longest. Due to its location, Japanese people enjoy seafood and vegetables on a daily basis; in addition, people there tend to be better at controlling the portion of their diets, helping them to live healthier than others. The other example that emphasizes the importance of healthcare systems in countries is Singapore. People in Singapore check for their health periodically, which helps in discovering chronic illness as well as ensuring overall health. As these three countries demonstrated above, having balanced diets and quality healthcare systems can help boost the overall life-expectancy of citizens. In addition, the reduction of inequality, social-political and economic improvement, female education, civil society organizations, political participation, and social security all reflect on a country's overall wealth and prosperity. The inequalities of wealth between countries have also led to the differences in life-expectancy. There's an example of how poverty influences life-expectancy. According to the data provided by the WHO, among the top 30 countries which have higher life-expectancies, most of them are from Europe, some of them are from Asia, North America, and Oceanic, but none of them are from Africa. Due to the harsh conditions African people live in, most people there are living in environments that hardly provide basic sanitation. Since it's hard for them to access clean water or fresh meals, the life-expectancy is unable to increase. For wealthier countries, on the contrary, they are able to provide higher standards of living for their citizens and invest more in healthcare systems to improve its efficiency. Only countries that are able to address these problems, could their citizens' overall life-expectancy increase. However, that doesn't mean that all wealthier countries tend to have higher life-expectancy, or countries that have lower income couldn't achieve higher life-expectancy; there're still a few exceptions such as the United States, which only has a 79.8, ranked at the 43th, and Jersey, which has a 81.9 of overall life-expectancy at the 18th. The overall life-expectancy, in fact, is truly based on the combination of these factors. Countries with lower income can also achieve higher life-expectancy by investing more in healthcare systems, committing to support the health of their people, ensuring social equality and community participation, and providing equivalent education opportunities for women. With effective policies issued to maintain the country's overall stability, the health of citizens could then be improved.

In terms of the discrepancy between genders' life expectancy, biology and psychology play a huge role. In general, females have higher life-expectancies than males. For almost all the countries listed above, females' life-expectancies in average are much higher than males'. mostly, as the histogram shows, females tend to have a 5–6 years more lifespan than males. The average of life-expectancy for males concentrates more on the range from 70.8 to 74.5 and reaches 85.6 as its highest, but for females, it concentrates more on the range from 76.50 to 80.75 and even reaches 93.5 as the highest. Many factors might contribute to this distinction, which are all influenced by the physiological and psychological differences between men and women. Females face a lower death rate; they have a second X chromosome which could compensate for the mutation of the first one – something that males (with only one X chromosome) can't. In addition, reproduction contributes to longevity – the needs of pregnancy prevents females from overeating; the estrogen they have is also believed to help protect them

from heart diseases. The testosterone, on the other hand, has contributed to violence and risky behaviors that males often take, like smoking, drinking, illegal abuse, and hazardous occupation. These behaviors eventually lead to a higher mortality rate(about 25–30 percent higher than females). However, the gap between females and males is narrowed in some underdeveloped countries.

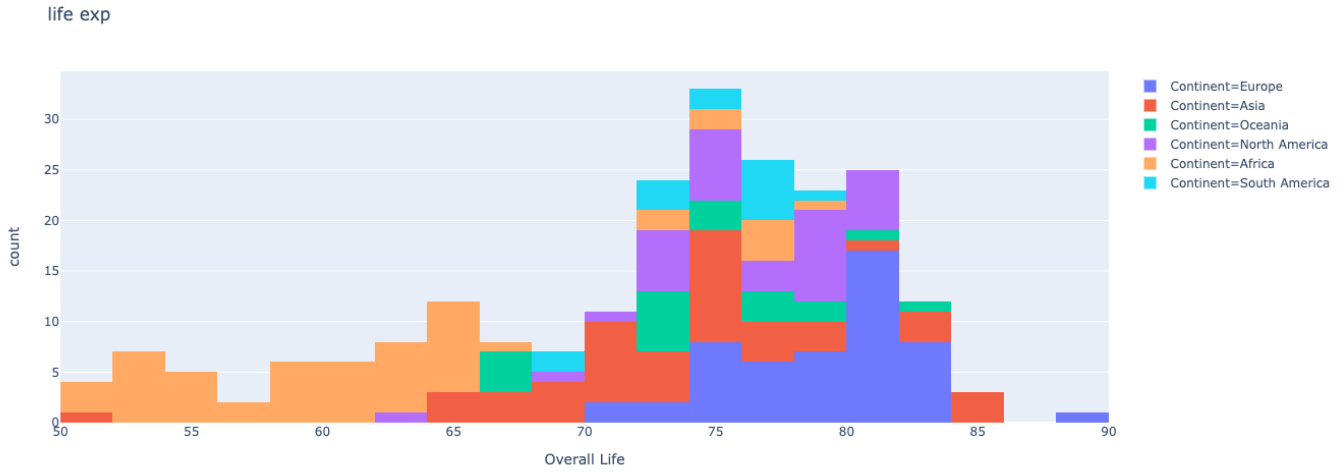


Figure 3. Histogram of overall life-expectancy colored by continent

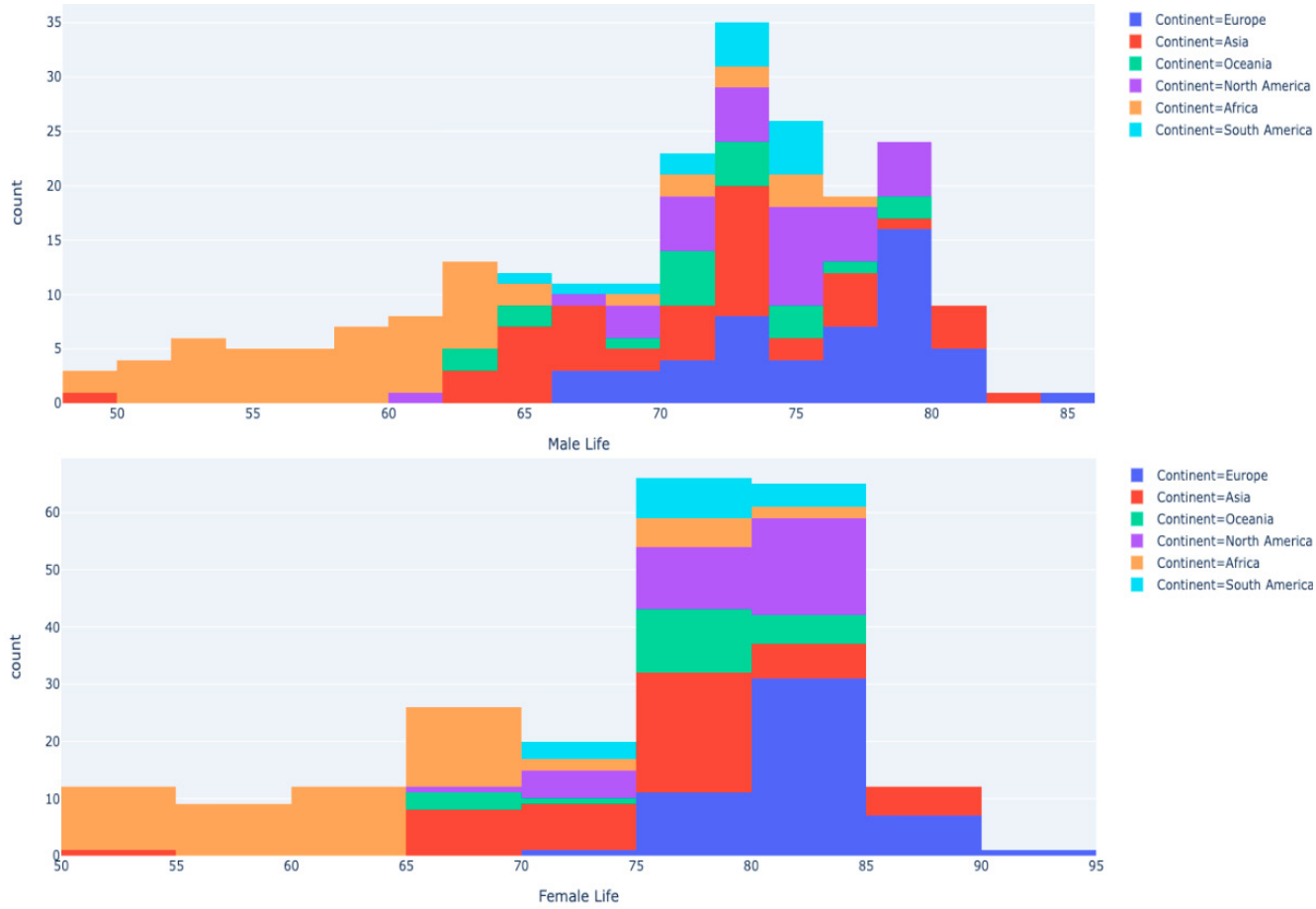


Figure 4. Histograms of female and male life expectancy colored by continent

As Figure 3 and Figure 4 show above, when the life expectancy of females and males has then been categorized based on the continents, it's clear that Africa and some parts of Asia have the lowest life expectancy, no matter for the graph of overall life, male life or female life. Part of this might be due to poverty which hinders countries from providing quality healthcare systems. It's obvious that Europe and some other parts of Asia have the highest life expectancy in either males or females, which exemplifies how prosperity of a country play a role here (and also the high level of economic inequality exists among Asian countries); despite that, in these underdeveloped countries, the equality among genders is still lacking, so the status of women might nullify the differences of life expectancy among genders as other countries might have. Females did not live longer than males, back in the 19th century; but in many countries nowadays, they outlive males, though they are more likely to become victims of crimes. This might largely be attributed to the social changes and progress. Women's status has been improved, which widens the female advantage in life expectancy. The social expectation towards masculinity gives rise to men's risky behaviors – like participating in dangerous jobs and engaging in perilous activities; women, however, who tend to overestimate the risk, are thus more likely to engage in deeper conversations with their doctors, which enables them to benefit from current medical advances and to prevent life threatening diseases. Compared to women, while having health issues, men are less likely to go to see a doctor, which prevents early detection and might even worsen their conditions – especially when dealing with mental illness. According to the research, people with severe mental health disorders might experience a 5–10 years reduction in longevity; it is important to talk about and share feelings, as most women do, when facing a problem; but as men often suffer from stress but tend to avoid communication, a higher suicide rate casued by their disengagement might then contribute to their higher mortality. In conclusion, there's not a single factor that could directly lead to the higher life expectancy of females; it is the combination of all the reasons mentioned above that contributes to this difference between genders, under the same living conditions.

Conclusion

Through analyzing the life expectancy based on the data provided by the WHO in groups, it has been found that the intersection of multiple factors might play a role in the disparity of life expectancy among humans. Differences among countries might be caused by their economic capability, effectiveness of the healthcare system, and living conditions and styles; differences between genders might be associated with physiological and psychological differences, gender roles, and personal characteristics. Only by understanding the differences and their causes, people could eventually address these issues and enjoy healthy and enriched lives.

References:

1. Freeman T., Gesesew H. A., Bambra C., Giugliani E. R. J., Popay J., Sanders D., … & Baum F. Why do some countries do better or worse in life expectancy relative to income? An analysis of Brazil, Ethiopia, and the United States of America. International journal for equity in health,– 19(1). 2020.– P. 1–19.
2. Stibich M. Learn How Aging Is Different for Men and Women. Verywell Health. January, 28. 2020. URL: https://www.verywellhealth.com/is-aging-different-for-men-and-women-2224332
3. Hull M. Mental Health's Impact on Life Expectancy. The Recovery Village Drug and Alcohol Rehab. November 29. 2021. URL: https://www.therecoveryvillage.com/mental-health/news/mental-health-impact-on-life-expectancy

4. Golden Charter. Which countries have the longest life span and why? | Golden Charter. Goldencharter. Co.Uk. January 24. 2017. URL: https://www.goldencharter.co.uk/news-and-info/2017/which-countries-have-the-longest-life-span-and-why
5. World Health Organization. (2018). Life expectancy and Healthy life expectancy, data by WHO region. WHO, Geneva [accessed 6 apr 2019]. URL: http://apps. who. int/gho/data/view. main. SDG-2016LEXREGv
6. Mayor E. Gender roles and traits in stress and health. Frontiers in psychology,– 6. 2015.– 779 p.
7. Desjardins B. Why is life expectancy longer for women than it is for men?. Scientific American,– 291(6). 2004.– P. 120–120.
8. Ortiz-Ospina E. & Beltekian D. Why do women live longer than men. Our World in Data. 2018.
9. Yin S. Gender disparities in health and mortality. Population Reference Bureau. 2007.
10. Assari S. If men are favored in our society, why do they die younger than women. The Conversation,– 8. 2017.
11. Luy M. & Minagawa Y. Gender gaps-Life expectancy and proportion of life in poor health. Health Reports,– 25(12), 2014.– 12 p.

Section 2. Physiology

https://doi.org/10.29013/ELBLS-22-1-20-25

Yiran Deng,
Ivymind Academy, PA, USA
E-mail: ydeng3373@gmail.com; xxjnicole@hotmail.com

CONCUSSIONS FROM PLAYING SPORTS AMONG HIGH SCHOOL STUDENTS

Abstract

Objective: This study aims to 1) examine the predictors of concussions from playing a sport 2) build a predictive model for concussions from playing a sport using logistic regression model.

Methods: Youth Risk Behavior Surveillance System (YRBSS) 2019 data were used for this study. All the participants who were eligible were randomly assigned into 2 groups: training sample and testing sample. Receiver operating characteristic (ROC) were calculated.

Results: About 13.31% of 5319 high school students had at least a concussion from playing a sport, about 12.45% among the female and 14.25% among the male.

According to the logistic regression, Q3 (In what grade are you), Q5 (What is your race?), Q6 (How tall are you without your shoes on), QN23 (During the past 12 months, have you ever been bullied on school property?), Q31 (How old were you when you first tried cigarette smoking, even one or two puffs?), Q41 (During the past 30 days, on how many days did you have at least one drink of alcohol?), Q60 (During your life, with how many people have you had sexual intercourse), Q81(In an average week when you are in school, on how many days do you go to physical education (PE) classes?), Q82 (During the past 12 months, on how many sports teams did you play? (Count any teams run by your school or community groups.)) were significantly associated with the concussions from playing a sport in the high school students.

The area under curve was 0.6837. The optional cutoff time is 0. 8342. The mis-classification error was 0.1339. The sensitivity rate is about 0.5% and the specificity is 99.95%.

Conclusions: In this study, we identified several important predictors for concussions from playing a sport e.g., race, been bullied, how many sports teams did you play on.

Keywords: Concussion, logistic regression, race, gender, sports.

1. Instruction

The Centers for Disease Control estimates more than 300,000 sports-related concussions occur each year in the United States. There are a number of myths and misunderstandings among health care professionals regarding concussions.

High school athletes are more vulnerable to concussions than older athletes and may take longer

to recover [1; 2; 3]. More than 5% of high school athletes are concussed each year while participating in collision sports [4].

In this study, we aim to: 1) examine the predictors of the having a concussion from playing a sport at high school; 2) build a predictive model for having a concussion from playing a sport using logistic regression model.

2. Data and Methods:

Data:

Youth Risk Behavior Surveillance System (YRBSS) 2019 data were used for this study.

The YRBSS was developed in 1990 to monitor priority health risk behaviors that contribute markedly to the leading causes of death, disability, and social problems among youth and adults in the United States.

Models:

We also used logistic regression models to calculate the predicted risk. Logistic regression is a part of a category of statistical models called generalized linear models, and it allows one to predict a discrete outcome from a set of variables that may be continuous, discrete, dichotomous, or a combination of these. Typically, the dependent variable is dichotomous and the independent variables are either categorical or continuous.

The logistic regression model can be expressed with the formula:

$$\ln(P/(1-P)) = \beta_0 + \beta_1 * X_1 + \beta_2 * X_2 + \ldots . + \beta_n * X_n$$

Model evaluation:

The discriminatory ability – the capacity of the model to separate cases from non-cases, with 1.0 and 0.5 meaning perfect and random discrimination, respectively– was determined using receiver operating characteristic (ROC) curve analysis. ROC curves are commonly used to summarize the diagnostic accuracy of risk models and to assess the improvements made to such models that are gained from adding other risk factors.

Outcome Variables:

The outcome variable is percentage of students who had a concussion from playing a sport (During the past 12 months, how many times did you have a concussion from playing a sport or being physically active) based on Q83.

3. Results

About 13.31% of 5319 high school students had at least a concussion from playing a sport, about 12.45% among the female and 14.25% among the male.

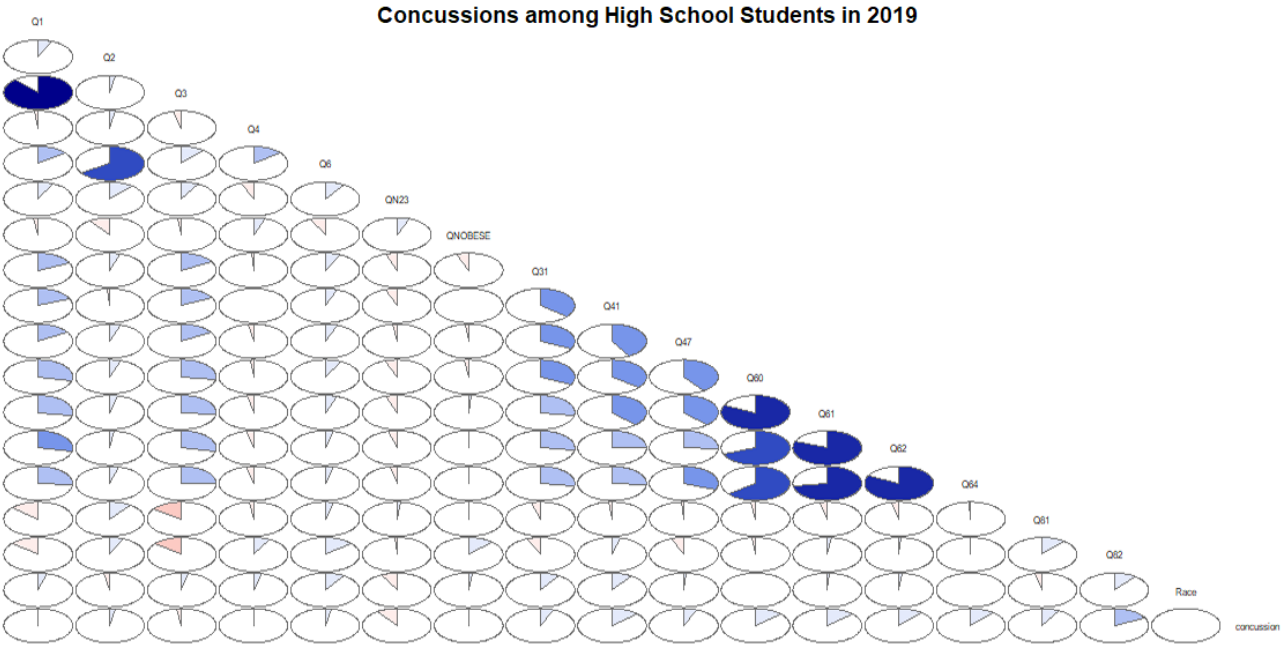


Figure 1. Matrix of correlations between variables

Basically, a corrgram is a graphical representation of the cells of a matrix of correlations. The idea is to display the pattern of correlations in terms of their signs and magnitudes using visual thinning and correlation-based variable ordering. Moreover, the cells of the matrix can be shaded or colored to show the correlation value. The positive correlations are shown in blue, while the negative correlations are shown in red; the darker the hue, the greater the magnitude of the correlation.

According to the logistic regression, Q3 (In what grade are you), Q5 (What is your race?), Q6 (How tall are you without your shoes on), QN23 (During the past 12 months, have you ever been bullied on school property?), Q31 (How old were you when you first tried cigarette smoking, even one or two puffs?), Q41 (During the past 30 days, on how many days did you have at least one drink of alcohol?), Q60 (During your life, with how many people have you had sexual intercourse), Q81(In an average week when you are in school, on how many days do you go to physical education (PE) classes?), Q82 (During the past 12 months, on how many sports teams did you play? (Count any teams run by your school or community groups.)) were significantly associated with the concussions from playing a sport in the high school students.

Table 1.– Logistic Regression for having a concussion from playing a sport

	Estimate	**Std. Error z**	**value**	**Pr(>|z|)**	
1	***2***	***3***	***4***	***5***	***6***
(Intercept)	–1.850	0.992	–1.865	0.062	
Q1	0.113	0.079	1.431	0.152	
factor(Q2)2	0.092	0.118	0.776	0.438	
factor(Q3)2	–0.118	0.142	–0.829	0.407	
factor(Q3)3	–0.161	0.196	–0.821	0.412	
factor(Q3)4	–0.703	0.264	–2.659	0.008	**
factor(Q3)5	–8.525	196.968	–0.043	0.965	
factor(Q4)2	0.060	0.120	0.500	0.617	
factor(Race)2	–0.438	0.299	–1.462	0.144	
factor(Race)3	–0.425	0.260	–1.636	0.102	
factor(Race)4	–0.090	0.389	–0.231	0.817	
factor(Race)5	–0.546	0.232	–2.352	0.019	*
Q6	–0.463	0.586	–0.790	0.430	
factor(QN23)2	–0.576	0.099	–5.794	0.000	***
factor(QNOBESE)2	–0.123	0.126	–0.974	0.330	
factor(Q31)2	0.635	0.305	2.081	0.037	*
factor(Q31)3	–0.142	0.359	–0.395	0.693	
factor(Q31)4	–0.192	0.253	–0.761	0.446	
factor(Q31)5	0.311	0.166	1.869	0.062	.
factor(Q31)6	–0.010	0.171	–0.059	0.953	
factor(Q31)7	0.337	0.267	1.260	0.208	
factor(Q41)2	0.458	0.114	4.025	0.000	***

1	*2*	*3*	*4*	*5*	*6*
factor(Q41)3	0.201	0.169	1.188	0.235	
factor(Q41)4	0.495	0.211	2.342	0.019	*
factor(Q41)5	1.044	0.287	3.634	0.000	***
factor(Q41)6	0.880	0.578	1.523	0.128	
factor(Q41)7	1.055	0.676	1.562	0.118	
factor(Q47)2	0.132	0.156	0.843	0.399	
factor(Q47)3	0.126	0.194	0.647	0.518	
factor(Q47)4	–0.320	0.262	–1.220	0.222	
factor(Q47)5	0.221	0.262	0.842	0.400	
factor(Q47)6	–0.256	0.261	–0.978	0.328	
factor(Q60)2	0.866	0.647	1.339	0.180	
factor(Q60)3	1.133	0.650	1.742	0.081	
factor(Q60)4	0.526	0.666	0.789	0.430	
factor(Q60)5	1.221	0.670	1.822	0.068	
factor(Q60)6	0.710	0.712	0.996	0.319	
factor(Q60)7	1.399	0.600	2.332	0.020	*
factor(Q61)2	–0.214	0.574	–0.373	0.709	
factor(Q61)3	–0.353	0.565	–0.625	0.532	
factor(Q61)4	–0.325	0.571	–0.569	0.569	
factor(Q61)5	0.222	0.609	0.365	0.715	
factor(Q61)6	0.559	0.763	0.733	0.463	
factor(Q61)7	–0.972	1.354	–0.717	0.473	
factor(Q62)2	–0.012	0.184	–0.063	0.950	
factor(Q64)2	–0.484	0.367	–1.318	0.188	
factor(Q64)3	0.044	0.337	0.132	0.895	
factor(Q64)4	–0.051	0.319	–0.160	0.873	
factor(Q64)5	0.277	0.419	0.661	0.508	
factor(Q64)6	0.260	0.484	0.536	0.592	
factor(Q64)7	–0.301	0.372	–0.811	0.417	
factor(Q81)2	0.637	0.230	2.776	0.006	**
factor(Q81)3	0.023	0.208	0.113	0.910	
factor(Q81)4	0.101	0.134	0.751	0.452	
factor(Q81)5	0.288	0.234	1.231	0.218	
factor(Q81)6	0.509	0.103	4.959	0.000	***
factor(Q82)2	0.757	0.120	6.328	0.000	***
factor(Q82)3	1.108	0.127	8.726	< 2e-16	***
factor(Q82)4	1.423	0.132	10.768	< 2e-16	***

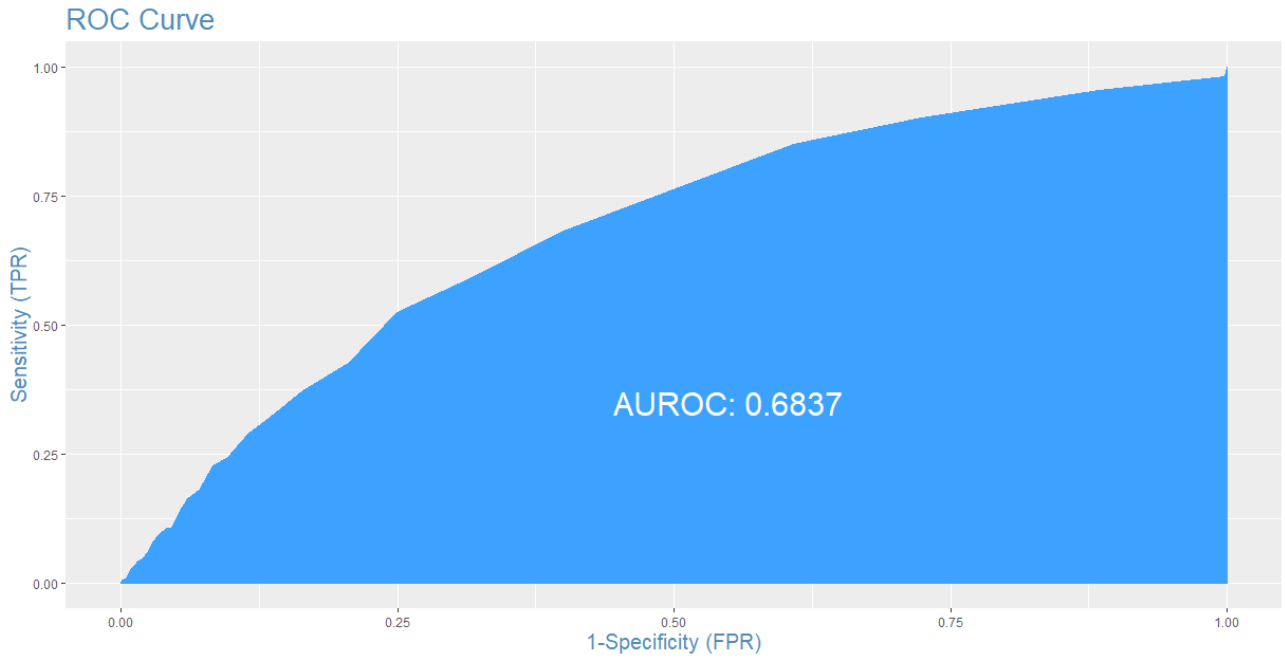


Figure 1. ROC in testing sample for Logistic Regression

The area under curve was 0.6837. The optional cutoff time is 0. 8342. The mis-classification error was 0.1339. The sensitivity rate is about 0.5% and the specificity is 99.95%.

Cut-off	sensitivity	specificity
0.5	4.2%	98.47%
0.7	0.8%	99.78%
0.9	0.3%	99.95%

4. Discussions

About 13.31% of 5319 high school students had at least a concussion from playing a sport, about 12.45% among the female and 14.25% among the male.

According to the logistic regression, Q3 (In what grade are you), Q5 (What is your race?), Q6 (How tall are you without your shoes on), QN23 (During the past 12 months, have you ever been bullied on school property?), Q31 (How old were you when you first tried cigarette smoking, even one or two puffs?), Q41 (During the past 30 days, on how many days did you have at least one drink of alcohol?), Q60 (During your life, with how many people have you had sexual intercourse), Q81(In an average week when you are in school, on how many days do you go to physical education (PE) classes?), Q82 (During the past 12 months, on how many sports teams did you play? (Count any teams run by your school or community groups.)) were significantly associated with the concussions from playing a sport in the high school students.

The area under curve was 0.6291. The optional cutoff time is 0.4876. The mis-classification error was 0.1335. The sensitivity rate is about 99.95% and the specificity is 0.8%.

In this study, we identified several important predictors for concussions from playing a sport e.g., race, been bullied, how many sports teams did you play on. A more systematic approach to this disorder needs to be considered to ensure that these vulnerable student athletes can participate safely in school sports [5].

References:

1. Lovell M. R., Collins M. W., Iverson G. L., Johnston K. M., Bradley J. P. Grade 1 or "ding" concussions in high school athletes. Am J Sports Med. 2004; 32: 47–54.
2. Mc Keever C. K., Schatz P. Current issues in the identification, assessment, and management of concussions in sports-related injuries. Appl Neuropsychol. 2003; 10: 4–11.
3. Webbe F. M., Barth J. T. Short-term and long-term outcome of athletic closed head injuries. Clin Sports Med. 2003; 22: 577–592.
4. Powell J. W., Barber-Foss K. Traumatic brain injury in high school athletes. JAMA. 1999; 282: 958–963.
5. Fred Theye and Karla A. Mueller. "Heads Up": Concussions in High School Sports. Clin Med Res. 2004. Aug; 2(3): 165–171.
6. Peng C. J., Lee K. L., Ingersoll G. M. An Introduction to Logistic Regression Analysis and Reporting. The Journal of Educational Research,– 96(1). – P. 3–14.
7. Tabachnick B. and Fidell L. Using Multivariate Statistics (4th Ed.). Needham Heights, MA: Allyn & Bacon, 2001.
8. Stat Soft, Electronic Statistics Textbook. URL: http://www.statsoft.com/textbook/stathome.html.
9. Stokes M., Davis C. S. Categorical Data Analysis Using the SAS System, SAS Institute Inc., 1995.

Section 3. Clinical Medicine

https://doi.org/10.29013/ELBLS-22-1-26-43

Mikheil Chkhaidze,
MD, PhDc, University of Georgia,
School of Health Sciences, PhD program in Public Health,
E-mail: mikheil.chkhaidze.phd@ug.edu.ge
Vasil Tkeshelashvili,
University of Georgia
MD, JD, PhD, ScD, Professor
E-mail: v.tkeshelashvili@ug.edu.ge

EVALUATION OF DEATH MECHANISMS IN TERMINAL PHASE OF CANCER

Abstract. Based on the primary site and degree of the cancer extension, epidemiological studies of incurable patients were initiated to examine mechanisms of death for determining the needs of cancer services and advocacy for terminal cancer patients, as well as to improve their insurance packages.

Keywords: Cancer, terminal phase, end of life, death mechanisms, cancer advocacy, Tbilisi, Georgia.

Relevance of the problem, research issues:

The geographic and gender distribution of cancer in key population centers, diagnosis, screening and early detection, treatment, 5-year survival and palliative care are well known in the world literature and are being studied today. Risks related to environment and lifestyle, cancer development, etc are also being studied. However, major attention is paid to physical and psycho-emotional condition of the patient, including evaluation of symptoms, etc [1–6, 10–44].

Thereby, less attention is paid to the study of the mechanisms of death of onco-incurable patients, the quality of life in their final years, months, and days of life, the protection of their needs and rights. To quote Jan Bohmann, "cancer kills with other hands" [7–9].

For advocacy of the patient having cancer in terminal phase, the following issues need to be additionally studied and verified due to significance and relevance of given aspects: verifying cancer incidence in Georgia and structure of the death caused by this reason according to the database of the cancer population-based registry;

Verifying the specific weight of thanatological care services for the patients in terminal phase of cancer; studying the death mechanisms of the patients and key reasons of death according to the primary sites and extension degree of the cancer; studying death signs and symptoms at the end of life of the onco-incurable patients; verifying activities necessary for improving life quality and thanatological care of the patients in terminal phase.

Purpose of the study:

Based on the primary site and degree of the cancer extension, studying of death mechanisms of patients, analyzing the activities necessary for improv-

ing life quality in the final days of life, supporting advocacy for terminal cancer patients, as well as to improve their insurance packages.

Study Objectives:

1. Defining the share of beneficiaries receiving referral services in palliative care facilities diagnosed with cancer in 2014–2021.
2. Defining the signs of disease progression in the terminal phase of cancer, defining the needs for palliative care and psychological support of patients by retrospective studying onco-incurable patients at the palliative care clinic, in Tbilisi, in 2019.
3. Verification of the mechanisms of death of patients and the main causes of their death according to the primary site and degree of cancer extension (by studying the histories of onco-incurable patients in palliative care clinics, in Tbilisi, in 2019);
4. According to the primary site and degree of cancer extension, studying of signs and symptoms of death at the end of life of patients (through prospective study of onco-incurable patients at palliative care clinics in Tbilisi, in 2021);

Target groups, studying tools and methodology:

In 2019–2021, a study was conducted to assess cancer-related deaths. First, the rates of all deaths incidence and dynamics were studied n Georgia (340,521 deceased citizens) and Tbilisi (88,025 deceased citizens) according to the absolute figures registered by Geostat in 2014–2020.

The electronic database of the National Center for Disease Control and Public Health (NCDC) in Georgia and Tbilisi was analyzed on the number of cancer beneficiaries receiving referral services in palliative care facilities in 2014–2021, respectively. In 2019, the last year before the COVID-19 pandemic, both in Georgia and in Tbilisi, the most complete registration data was reported compared to other years: about all death, cancer-related deaths, and the beneficiaries receiving referral services in palliative care facilities in the terminal stage of cancer.

In the first place, a retrospective study was conducted to assess the death mechanisms of patients in the terminal phase of cancer. The medical histories of patients admitted to the palliative clinic of JSC "Universal Medical Center" in 2019 were studied through a custom questionnaire. Information on 150 cancer (study group) and 150 neurological (control group) patients were retrospectively obtained in the terminal phase. An electronic database was created using retrospectively retrieved data from the questionnaire.

A prospective study was conducted in Phase 2 to evaluate the death mechanisms of patients in the terminal stage of cancer. In Acad. Z. Kakhiani Clinic Red (2021) conducted the study of the final days of 94 patients in terminal phase of cancer (key study group – 50 patients) and circulatory-neurological (control group- due to cerebrovascular stroke, mostly in patients with the comatose condition, patients without cancerous intoxication – 44). When monitoring terminal patients, vital signs were recorded for each patient using a custom questionnaire with variable registration. An electronic database was created using retrospectively retrieved data from the questionnaire. Databases were processed using SPSS software package.

The key findings of the study:

According to GeoStat, in this 7-year period (2014–2020), a total of 340,521 all deaths were reported in Georgia, including 88,025 in Tbilisi. In Georgia, an average of 48,646 deaths were reported every year for all causes, and 12,575 in Tbilisi.

In the first year of the COVID-19 pandemic (2020), in the 6-year period prior to the pandemic (2014–2019), the average standard annual mortality rate for all causes exceeded 2,206 cases in Georgia, including 1,520 in Tbilisi and 686 in the regions.

In the 1st year of the COVID-19 pandemic (2020), the expected increase in the number of deaths in Tbilisi and the regions is probably related to COVID-19, which is consistent with the data of the Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs (12.06.2021, https://www.moh.gov.ge/): the

total number of deaths due to COVID-19 reached 2505 in 2020. Unfortunately, it is not possible to identify Tbilisi inhabitants among them.

The average annual death rate caused by cancer in 2018–2019 was 4255.0 ± 96.2 in Georgia. The annual average rate of deaths caused by cancer in 2018–2019 was 1476.0± 5.7 in Tbilisi.

Prior to the COVID-19 pandemic, every year (2018–2019), the specific weight of death caused by cancer within the structure of all deaths, was 9% in Georgia, and in the 1st year of the pandemic (2020), it was 5%.

In 2018–2019, in total (all causes), an average of 46,591 deaths were registered annually in Georgia, including 4,255 (9%) caused by cancer and 42,336 (91%) for all other causes.

In 2020, 50,537 total deaths were registered in Georgia, including 2,405 (5%) caused by cancer and 48,132 (95%) due to all other causes.

Prior to the COVID-19 pandemic in Tbilisi, every year (2018–2019), the specific weight of death caused by cancer within the structure of all causes of death was 12%, and in the 1st year of the pandemic (2020) – 6%.

In 2018–2019, annually, an average of 12,335 total deaths were registered in Tbilisi, including 1,476 (12%) caused by cancer and 10,859 (88%) for all other causes.

In 2020, 13,878 total deaths were registered in Tbilisi, including 801 (6%) caused by cancer and 13,077 (94%) due to all other causes.

In Georgia and Tbilisi, respectively, in the period of 2014–2021, the dynamics of the number of beneficiaries receiving referral services and the dynamics of death in palliative care facilities were studied. In 2019, a total of 469 patients diagnosed with cancer in palliative care facilities received referral services, whereas 51 (10.9%) patients received palliative care, and the majority, 418 (89.1%) patients received thanatological. A total of 239 patients received referral services in Tbilisi, whereas 18 (7.5%) patients received palliative care, and the majority – 221 (92.5%) patients received thanatological. In 2019, the last year before the COVID-19 pandemic, the most complete census data was recorded compared to other years both in Georgia and in Tbilisi: about all deaths and cancer deaths, and beneficiaries receiving referral services in palliative care facilities at the terminal stage of cancer.

In 2019, only 10% of patients having terminal cancer in Georgia received referral thanatological services in palliative care facilities, while the number of recipients of similar services in Tbilisi was 15%. So, the majority of patients in the terminal stage of cancer (85–90%) died at home without receiving referral oncological care.

In Georgia, palliative care (84.6% of cases), including thanatological (85.9% of cases) and palliative (74.5%) referral services for patients were mainly provided in Tbilisi palliative clinics.

In Tbilisi, palliative care (41.6% of cases), including thanatological (42.6% of cases) and palliative (34.2%) referral services for patients were mainly provided at JSC "Universal Medical Center". Thereby, the following 5 clinics from 39 clinics in Tbilisi, provided 70.2% of palliative care referral services in 2019:

1. JSC Universal Medical Center – 41.8%
2. Tbilisi Oncology Dispensary Ltd – 9.8%
3. Academician Fridon Todua Medical Center Ltd – 8.8%
4. LEPL L. Sakvarelidze National Center for Disease Control and Public Health – 5.8%
5. Academician Z. Kakhiani Clinic Red Ltd – 4.0%

In 2019, a total of 46,569 patients died in Georgia, including 4,187 (9%) deaths were caused by cancer, of which only 418 (0.9%) received referral services in palliative care facilities, which is only 10% of cancer deaths in Georgia.

In the first place, a retrospective study was conducted to assess the death mechanisms of patients in the terminal phase of cancer. The medical histories of patients admitted to the palliative clinic of JSC "Universal Medical Center" in 2019 were studied

through a custom questionnaire. Information on 150 oncology (study group) and 150 neurological (control group) patients were retrospectively obtained in the terminal phase. In 1 (0.7%) of the oncology patients, the disease was registered in the 3rd, and in 149 (99.3%) cases – in the 4th clinical stage. Of these, 15 patients (10.0%) were physically fit for ECOG-3 and 135 (90.0%) for ECOG-4. The physical condition of 8 patients (5.3%) in the control group corresponded to ECOG-3 and 142 (94.7%) to ECOG-4. There was no statistically reliable difference between the study and control groups according to ECOG status (Chi_2 = 2.3; p = 0.128). In the study group, 80 (53.3%) patients were male and 70 (46.7%) were female, while in the control group 54 (36.0%) patients were male and 96 (64.0%) were female. The avarage age of patients in the study group was 65.9 years, and in the control group – 76.1 years.

The same frequency was observed in the two groups with low values of body mass index, normal body temperature, blood pressure below the norm (systolic and diastolic), increased pulsation, increased respiration, decreased saturation, and nighttime sleep duration.

HCV occurs with equal frequency In the history of oncological and neurological patients in the terminal phase. It is noteworthy that history reports HCV in both groups in more than 4/5 of patients! There was also no statistically significant difference between HCV frequencies in cancer patients by gender and primary localization of cancer. The study of the role of HCV in the thanatogenesis of patients in the terminal phase requires further studies.

Primary cancer in male patients was mainly localized in lungs (32%), digestive organs (15%), liver (11%), urogenital organs (14%).

Initial cancer in female patients is mainly localized in the organs of the reproductive system (50%), including genitals (26%) and breast (24%), as well as in the organs of the digestive system (23%).

There was also no statistically significant difference between the incidence of HCV in cancer patients by gender and by the initial localization of cancer.

The physical condition of the patients in the terminal phase was analyzed according to the basic systems.

Spontaneous respiration was observed in 29% of patients in the study group and 52% in the control group. Vesicular and impaired vesicular respiration was observed in 25% and 36% of patients, and 40% and 3% in the control group, respectively. In cancer patients, vesicular and impaired vesicular respiration was statistically more likely (Chi_2 = 19.40; p <0.001) to occur more frequently (2.2 times) in male patients (55%) than in women (25%); this is possibly related to the circumstance that male patients had a higher incidence of lung cancer than female patients.

89.3% of cancer patients had dyspnoea (shortness of breath accompanied by air insufficiency), 70.0% – shortness of breath, 84.7% – difficulty breathing (due to excessive exudate or ascites), and 58, 0% showed dry, non-stop coughing.

55.6% –81.8% of oncology patients had shortness of breath according to the primary localization of cancer. At the same time, the probability of shortness of breath was 3.5 times higher in cancers of the digestive tract compared to breast cancer (OR = 3.5; 95% CI OR = 1.1–10.9).

Non-persistent dry cough, in digestive cancer, was 2.9 times more common than during lung cancer (OR = 2.9; 95% CI OR = 1.1–7.6), 3.5 times more common in breast cancer (OR = 3.5; 95% CI). OR = 1.2–10.4) and in urological cancer (OR = 3.5; 95% CI OR = 1.1–11.1). Non-persistent dry cough in liver cancer is 4.5 times more likely than in breast cancer (OR = 4.5; 95% CI OR = 1.04–20.2).

64.0% of oncology patients had shortness of breath, sometimes prolonged pauses between breaths, noisy breathing with interruptions and anxieties or changing tone of voice, 22.7% showed cough with bloody and mucous sputum, 82.0% – pleura accumulation, and 87.3% of them showed changes in

breathing, mouth breathing becomes irregular and noisy, which stops at some point.

According to the primary localization of cancer, coughing with bloody and mucous sputum was most frequently observed in cancers of the lung (32.3%) and digestive organs (29.6%). At the same time, the incidence of cough with bloody and mucous sputum in cancer of the digestive organs is 6.2 times higher than in urological cancer (OR = 6.2; 95% CI OR = = 1.01–54.2).

Accumulation of exudate in the pleura according to the primary localization of cancer was observed with the highest frequency in cancers of the digestive organs (92.6%) and lungs (90.9%). At the same time, the probability of exudate accumulation in the pleura during cancer of the digestive organs is 5.0 times higher compared to urological cancer (OR = 5.0; 95% CI OR = 1.06–23.6).

In the terminal phase, in 78.0% of oncology patients, Cheyne-Stokes respiration was observed, in 2.7%, terminal secretion (death rattle) was reported, and in 13.3%, stopping of breathing was reported.

Stopping of breathing in the terminal phase was observed in 78.7% of male patients and 67.1% of female patients in the study group (Chi2 = 2.01; p = 0.022). The risk of stopping breathing in the terminal phase was 3 times higher in men than in female patients (OR = 3.00, 95% CI OR = 1.03–8.74).

44.0% of oncology patients had a chronic cardiovascular failure, 39.3% – acute cardiovascular failure. Thus, in 83.3% of patients, the disease progresses amidst cardiovascular failure in the terminal phase, and in 70% of cases, the patients develop syncope.

The incidence of chronic cardiovascular failure in urological cancer is 3.9 times higher than in cancer of the digestive organs (OR = 3.9; 95% CI OR = 1.2–12.5).

According to the primary localization of cancer, in the terminal phase, mean systolic and diastolic blood pressure readings of patients in both the study and control groups were observed lower than the normal limit and no statistically significant difference was found between the study and research groups (p> 0.05). This is logical, given the circumstances that the death of patients is preceded by a fall in blood pressure.

At the same time, according to the primary localization of cancer in the study group, patients in the control group had tachycardia, and no statistically reliable difference was found between the study and research groups (p> 0.05), which is logical given the fact that patients showed lowered saturation in the terminal phase and, consequently, the tachycardia had a compensatory character.

The risk of developing syncope in lung cancer was 2.7 times higher than in cancer of the digestive organs (OR = 2.7; 95% CI OR = 1.1–8.6).

100% of cancer patients continued to take food for almost the rest of their lives and 98.0% of them had gastric activity.

In the terminal phase, 82.7% of oncology patients showed decreased appetite, 80.7% – dysphagia, 81.3% – weight loss, 78.0% – abrupt weight loss and muscle wasting, 86.7% had cachexia, confirmed by BMI.

67.3% of oncology patients had dry mouth and lips, 59.3% – nausea, and 48.7% – vomiting. At the same time, 63.3% of oncology patients had constipation, 28.7% had diarrhea, 38.7% had an obstruction caused by tumor compression, and 46.0% had lost control of gastric activity.

The probability of constipation in the terminal phase was 3.8 times higher in digestive organ cancer compared to urological cancer (OR = 3.8; 95% CI OR = 1.2–12.0).

Compared to cancer of the digestive organs, the frequency of obstruction due to tumor compression, the probability of obstruction due to metastatic tumor compression was 4.2 times higher than in case of lung cancer (OR = 3.8; 95% CI OR = 1.4–12.5), 3.7 times – breast cancer (OR = 3.7; 95% CI OR = 1.1–14.3), 3.3 times – gynecological cancer (OR = 3.3; 95% CI OR = 1.02–14.3) and 4.4 times – urological cancer (OR = 4.4; 95% CI OR = 1.2–16.7).

In breast cancer cases, the likelihood of diarrhea was 4.4 times higher compared to lung cancer (OR = 4.4; 95% CI OR = 1.5–12.5), 3.3 times higher – cancer of the digestive organs (OR = 3.3; 95% CI OR = 1.2–11.1), and 3.5 times – gynecological cancer (OR = 3.5; 95% CI OR = 1.1–11.1).

In the frequencies of loss of control over gastric action, according to the primary localization of cancer, no statistical difference (p> 0.05) was reported.

In cases of liver cancer, the probability of developing ascites was 7.7 times higher than in cancers of other organs of the digestive system (OR = 7.7; 95% CI OR = 1.3–50.0).

In the terminal phase, 82.7% of oncology patients showed decreased appetite, 80.7% – dysphagia, 81.3% – weight loss, 78.0% – abrupt weight loss and muscle wasting, 86.7% – cachexia, confirmed by BMI.

In cases of breast cancer, the probability of increased weakness and exhaustion was 10.0 times higher compared to urological cancer (OR = 10.0; 95% CI OR = 1.6–99.9), 3.6 times – cancer of the digestive organs (OR = 3.6; 95% CI OR = 1.14–11.1) and 7.7 times compared to liver cancer (OR = 7.7; 95% CI OR = 1.2–99.0).

63.3% of oncology patients showed constipation, 28.7% – diarrhea, 38.7% – obstruction due to tumor compression, and 46.0% – lost control of gastric activity.

In cases of lung cancer, the probability of developing dry mouth and lips during lung cancer (80.6%) was 3.3 times higher compared to breast cancer (OR = 3.3; 95% CI OR = 1.1–9.8), 3.0 times higher -gynecological cancer (OR). = 3.0; 95% CI OR = 1.04–8.8) and 4.2 times compared to urological cancer (OR = 4.2; 95% CI OR = 1.3–13.2).

In cases of cancer of the digestive organs, the probability of decreased appetite was 10.4 times higher than in urological cancer (OR = 10.4; 95% CI OR = 1.5–72.2).

The incidence of dysphagia according to the primary localization of the cancer is shown in Figure 94. Thereby, the probability of dysphagia compared to liver cancer was 4.3 times higher in lung cancer (OR = 4.3; 95% CI OR = 1.2–15.6), 6.7 times higher in breast cancer (OR = 6.7; 95% CI OR = 1.4–32.5) And 5.0 times in urological cancer (OR = 5.0; 95% CI OR = 1.01–24.8).

Loss of control over gastric function in the terminal phase was observed in 40.0% of male cancer patients and 52.9% of female patients (Chi2 = 1.57; p = 0.058).

At the same time, the risk of losing control of gastric function was 1.7 times higher in female patients (OR = 0.60, 95% CI OR = 0.31–1.14).

Ascites was reported in 68.7% of cases, fever in 67.3%, and liver failure in 83.3%. Catastrophic bleeding from the abdominal organs was not observed in any case.

In the terminal phase, oncology patients had a liver failure in 88.1% of cases with fever, while liver failure during the course of the disease without the fever was observed in 73.5% of cases (Chi2 = 5.10; p = 0.024).

In the terminal phase, the probability of fever in breast cancer was 4.0 times higher than in cancer of the digestive organs (OR = 4.0; 95% CI OR = 1.1–18.8), and in gynecological cancer, the probability of fever was 9.0 times higher compared to breast cancer (OR = 9.0; 95% CI OR = 1.4–58.9).

The risk of liver failure in the terminal phase was 4.0 times higher than in breast cancer (OR = 4.0; 95% CI OR = 1,1–18,8) and 9.0 times higher in gynecologic cancer (OR = 9.0; 95%). CI OR = 1.4–58.9).

In the terminal phase, oncology patients accumulated fluid in the abdomen in 74.3% of cases with fever, while ascites was observed in 57.1% cases without the fever (Chi2 = 4.49; p = 0.034).

In the terminal phase, fever was observed in 40.0% of males and 52.9% of women (Chi2 = 1.78; p = 0.037).Thereby, amidst terminal phase fever, the risk is 1.9 times higher in women than in men (OR = =1.9; 95% CI OR = 1.04–3.7).

Tumor intoxication is observed with high frequency in all studied localizations of cancer, especially in cases of liver cancer (100.0%).

The amounts of fluid received and excreted from the urine during the day and night were studied in the study and control groups.

The difference between the amounts of fluid received and excreted in 24 hours averaged 183.7 ml in cancer patients and 158.5 ml in the control group. That is, in cancer patients, compared to the control group, more than 25.2 ml of fluid per day were accumulated in the body, which is probably associated with the development of ascites and/or exudative pleurisy and/or swelling of the lower extremities in cancer patients (Z-test = –1.65; p =.049).

34.2 ml more fluid was accumulated in the body of male cancer patients daily than in female patients. The difference between the amounts of fluid accumulation in the body by sex is statistically reliable (Z-test = –2.01; p = 0.022). The difference between the daily fluid balance and the amount of fluid accumulated in the body according to the primary localization of the cancer was not statistically reliable (p> = 0.05).

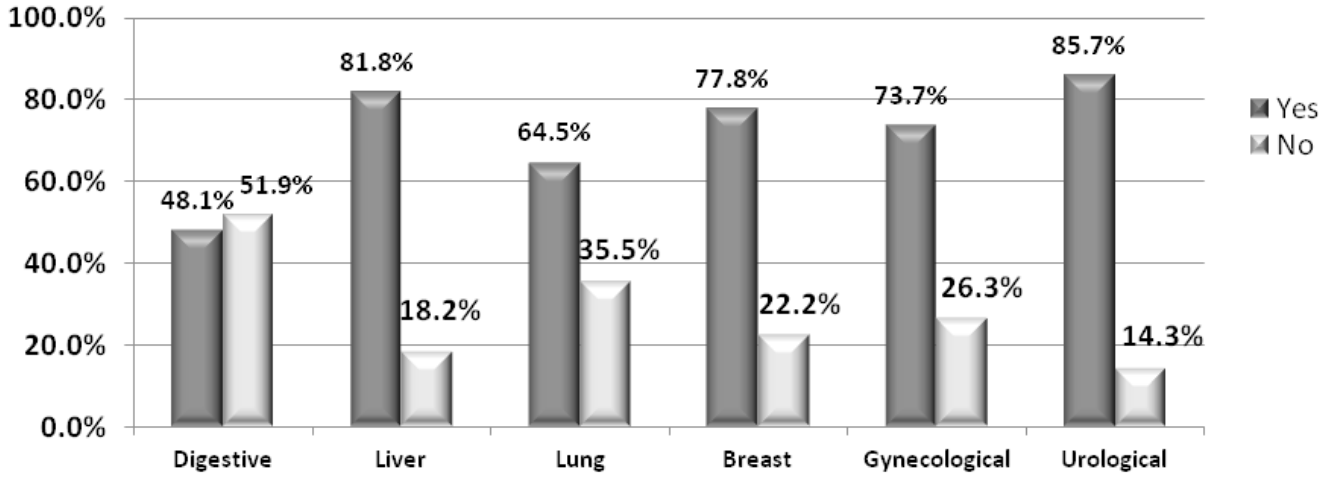
83.3% of cancer patients in the terminal phase had urination complaints, 88.7% – a decrease in the amount of excreted urine, 71.3% – tumor compression of the urinary tract (urethra, bladder or urethra), 78.7%% – renal failure, 68.0% – swelling of the lower extremities, 80.7% uremia.

Urination complaints, symptoms according to the primary localization of the cancer are shown in Figure 110. At the same time the probability of urinary disorders compared to breast cancer is 4.0 times higher than cancer of the digestive organs (OR = 4.0; 95% CI OR = 1.1–18.8), 3.4 times – lung cancer (OR = 3.4; 95% CI OR = 1.01–11.2) and 9.0 times higher in gynecological cancer (OR = 9.0; 95% CI OR = 1.4–59.0).

A frequent decrease in the amount of urine excreted is observed in all studied localizations of cancer, especially in cases of urological cancer (92.9%).

Compared with cancer of the digestive organs, the risk of developing tumorous compression of the urethra, bladder or urethra is 9.0 times higher in urological cancer (OR = 9.0, 95% CI OR = 1.6–33.3), 4.8 times – in liver cancer (OR = 4.8, 95% CI OR = 1.1–11.1), 3.7 times in breast cancer (OR = 3.7, 95% CI OR = 1.02–14.3) and 3.0 times in gynecological cancer (OR = 3.0, 95% CI OR = 1.04–11.1).

Figure 1. In the terminal phase of cancer, tumorous compression of the urethra, bladder, or urethra according to the initial localization of the cancer



Source: study findings

64% of oncology patients had normal skin color, while 36% had anemic, bluish, dark brown, grayish-yellow, yellowish, or greenish, and while the majority of patients in the control group (99%) had anemic skin color.

61% of men with cancer had normal skin color, and 39% had anemic, bluish, dark brown, grayish-yellow, yellowish, or greenish color, while 66% of women had normal skin color and 34% had abnormal coloration.

No statistically reliable difference was found in the skin color of cancer patients by sex (Chi2 = –0.53; p = 0.297).

Compared to cancer of the digestive organs, the probability of other skin colors (gray, yellowish, greenish) is 4.4 times higher in breast cancer (OR = 4.4; 95% CI OR = 1.4–13.6) and 3.7 times higher in liver cancer (OR = 3.7; 95%). CI OR = 1.01–13.3).

In cancer of the digestive organs, the probability of yellowing of the skin and eyes is 6.3 times higher than in breast cancer (OR = 6.3; 95% CI OR = 1.5–27.0) and 6.9 times higher than in urological cancer (OR = 6.9; 95% CI OR = 1.5). 71.7), and the probability of yellowing of the skin and eyes in lung cancer is 15.0 times higher than in breast cancer (OR = 15.0; 95% CI OR = 1.6–138.0) and 16.7 times higher than in urological cancer (OR = 16.7; 95% CI OR = 2.5–112.2).

Compared to digestive cancers, skin rashes or itching are 3.3 times higher in breast cancer (OR = 3.3; 95% CI OR = 1.2–11.1), 4.6 times higher in gynecological cancer (OR = 4.6; 95% CI OR = 1.3–16.7) and 4.8 times higher – in urological cancer (OR = 4.8; 95% CI OR = 1.5–14.3).

Skin temperature in the case group was normal in only 17%, it was chilly in 74% (66%) or cold (8%), and hot in 9%, especially on the hands and feet, while the skin temperature in 100% of the control group was chilly.

The skin temperature of men in cancer patients was normal in 19% of cases, chilly in 74% (65%) and cold in 9%, and hot in 7%, especially on the hands and feet.

The skin temperature of women oncology patients was normal in 14% of cases, chilly in 78% (67%), cold (9%), and hot in 10%, especially on the hands and feet.

When metastases develop in bone, abnormal fractures develop in 19.2% of cases, while abnormal bone fractures without cancer metastases occur in only 6.5% of cases, and this difference is statistically reliable (Chi2 = 5.45; p = 0.020).

Abnormal fractures were observed with a higher frequency in male (18.8%) than female (5.7%) patients. Male patients have a 3.8 times higher risk of abnormal fractures (OR = 3.8; 95% CI OR = 1.2–12.1; Chi2 = 2.27; p = 0.012).

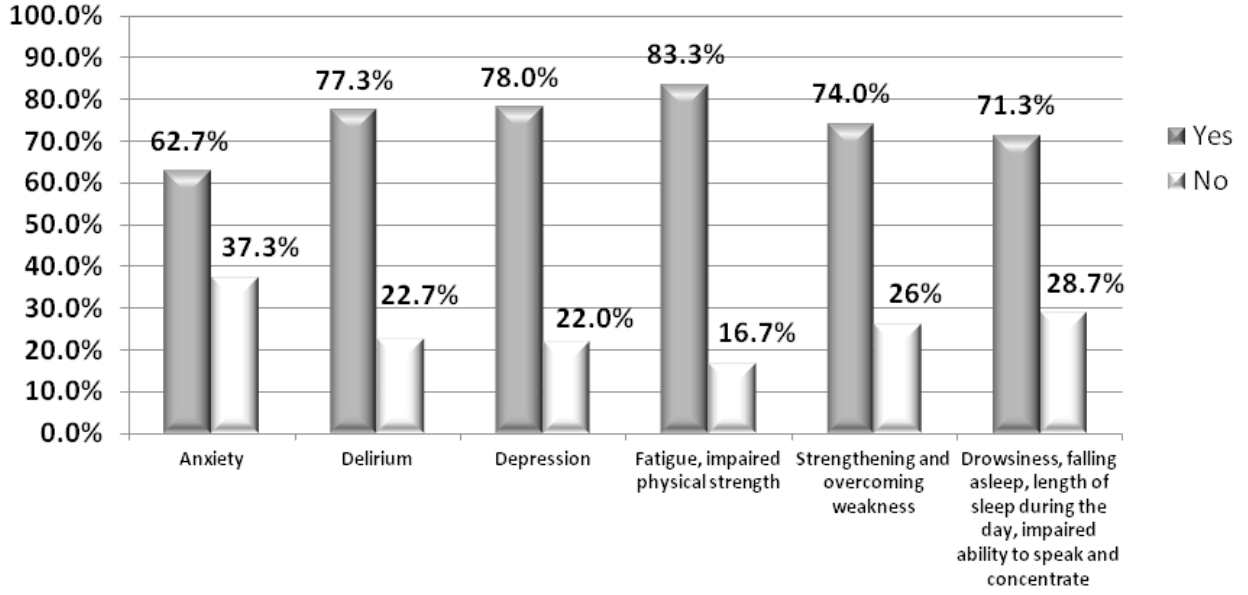
The risk of abnormal fractures in breast cancer is 3.6 times higher than in cancers of the digestive organs (OR = 3.6; 95% CI OR = 1.1–11.1) and 10.0 times higher than in urological cancers (OR = 10.0; 95% CI OR = 1.6–99.9), and The probability of abnormal fracture compared to breast cancer was 7.7 times higher in patients diagnosed with liver cancer (OR = 7.7; 95% CI OR = 1.2–99.0).

The probability of metastases in the bones during breast cancer and the related severe pain is 2.9 times higher compared to the digestive organs (OR = 2.9; 95% CI OR = 1.02–10.1) and 3.4 higher in gynecologic cancer (OR = 3.4; 95% CI OR = 1.1). 10.7), and compared to liver cancer, metastases in the bones and the related severe pain are 3.7 times higher in lung cancer (OR = 3.7; 95% CI OR = 1.04–16.7), 4.8 times higher in urological cancer (OR = 4.8; 95% CI OR = 1.1–20.0) and 5.3 times in breast cancer (OR = 5.3; 95% CI OR = 1.02–33.3).

It is very important and interesting to assess the psycho-emotional state of terminal cancer patients.

62.7% of terminal oncology patients experienced anxiety, 77.3% – delirium, 78.0% – depression, 83.3% – fatigue, exhaustion, decreased physical strength, 74.0% – increasing of weakness and exhaustion, and 71.3% – drowsiness, falling asleep throughout the day, impaired ability to speak and concentrate.

Figure 2. Factors reflecting the psycho-emotional state of patients in the terminal phase of cancer



Source: Study findings

Anxiety in the terminal phase is observed in patients in 70.4% of cases of digestive cancer, liver cancer – in 54.5%, lung cancer – in 77.4%, breast cancer – in 50%, gynecological cancer – in 73.7%, urological cancer – in 64.3%.

Delirium in the terminal phase occurs in patients with 66.7% of cases of digestive cancer, liver cancer – 90.9%, lung cancer – 83.9%, breast cancer – 66.7%, gynecological cancer – 84.2%, urological cancer – in 64.3%.

Terminal phase depression occurs in 88.9% of cases of digestive cancer, liver cancer – 90.9%, lung cancer – 87.1%, breast cancer – 61.1%, gynecological cancer – 73.7%, urological cancer – 71.4%.

Fatigue, exhaustion, impaired physical strength appears in 76.3% of men with cancer and 91.4% of women with cancer. The difference between the frequencies of this symptom by sex is statistically reliable (Chi2 = 2.40; p = 0.008). Fatigue, exhaustion, impaired physical strength are 3.3 times more common in women with cancer (OR = 0.3; 95% CI OR = 0.11–0.80).

Fatigue, exhaustion, impaired physical strength in the terminal phase are observed in patients with 96.3% of digestive cancer cases, liver – 72.7%, lung – 87.1%, breast – 77.8%, gynecological – In 89.5%, urological in 85.7%.

81.3% of terminal oncology patients gradually become less sensitive to touch or sound, 88.0% – lose sensitivity to skin contact, 72.7% experience confusion and disorientation, 12.0% experience myoclonus, and 6, 7% shows complete loss of consciousness.

Drowsiness, falling asleep, prolonged sleep during the day, impaired ability to speak and concentrate in the terminal phase are observed in patients with 81.5% of cases of digestive cancer, liver cancer – 63.6%, lung cancer – 71.0%, breast cancer – 61 In 1%, gynecological cancer – 73.7%, urological cancer – 78.6%.

Lack of interest in the issues that were previously important to him/her, loss of interest in the outside world, and ongoing events are observed in the terminal phase, in 51.9% of cases of digestive cancer, liver cancer – 72.7%, lung cancer – 58.1%, breast cancer – in 61.1%, gynecological cancer – 78.9%, urological cancer – 50.0%.

The desire to be with only a few dearest people and to limit the time spent with visitors are observed in patients with 77.8% of cases of digestive cancer, liver – with 81.8%, lung – with 64.5%, breast – in

44.4%, gynecological – in 63.2%, urological in 42.9%, in the terminal phase.

Restlessness or repetitive, involuntary movements in the terminal phase are observed in patients in 77.8% of cases of digestive cancer, liver – in 72.7%, lung – in 64.5%, breast – in 66.7%, gynecological – 68 in 4%, urological in 64.3%.

Confusion/feeling of losing in time, place, uncertainties in personalities, including family members and close friends, occurs in 74.1% of cases of digestive cancer, 63.6% of liver, 67.7% of lung, 88.9% of breast cancer, 68.4% of gynecological cancer, 71.4% of urological cancer, in the terminal phase.

He/she hears or sees people or things that are not there. These ghosts (?) often include greetings with the deceased people and these are reported in the terminal phase, in patients in 33.3% of cases of digestive cancer, liver – in 36.4%, lung – in 45.2%, breast – in 44.4%, Gynecological – in 63.2%, urological in 57.1%.

The tendency of losing and regaining consciousness in the terminal phase is observed in patients with 55.6% of cases of digestive cancer, liver – 63.6%, lung – 64.5%, breast – 72.2%, gynecological – 73,7%, urological – 64.3%.

The patient gradually becomes less sensitive to touch or sound in the terminal phase, which is reported in patients of 77.8% of cases of digestive cancer, liver – 90.9%, lung – 83.9%, breast – 77.8%, Gynecological – 84.2%, urological 85.7%.

Complete loss of consciousness in the terminal phase is observed in patients of 14.8% of cases of digestive cancer, liver – 9.1%, lung – 3.2%, breast – 11.1%, gynecological – 5.3%, urological 0%.

64.0% of cancer patients in the terminal phase lose interest in the issues that were important to them, 63.3% have a desire to be close to only a few dearest people and limit the time spent with others, 68.0% have restlessness or recurrent, involuntary movements.

Confusion and disorientation in the terminal phase are observed in patients in 74.1% of cases of digestive cancer, liver – 81.8%, lung – 83.9%, breast – 55.6%, gynecological – 68.4%, urological 71.4%.

Myoclonus occurs in 16.3% of men with cancer and 7.1% of women with cancer. The difference between the frequencies of this symptom by sex is statistically reliable (Chi2 = 1.67; p = 0.048). Myoclonus is 2.5 times more common in men with cancer (OR = 2.5; 95% CI OR = 1.02–7.42).

Myoclonus in the terminal phase occurs in patients with 7.4% of cases of digestive cancer, liver – 9.1%, lung – 19.4%, breast – 5.6%, gynecological – 5.3%, urological – 14.3%.

Changes in vision, in the terminal phase, are observed in patients in 63.0% of cases of digestive cancer, liver – 72.7%, lung – 58.1%, breast – 77.8%, gynecological – 68.4%, urological 71.4%.

Hearing problems, in the terminal phase, occur in patients in 63.0% of cases of digestive cancer, liver – 72.7%, lung – 54.8%, breast – 66.7%, gynecological – 73.7%, urological 64.3%.

Problems with balance or dizziness, in the terminal phase, occur in 74.1% of cases of digestive cancer, 63.6% of liver, 80.6% of lung, 66.7% of breast, 78.9% of gynecological, and 71.4% of urological cancers.

Mood or personality changes, in the terminal phase, are observed in patients in 81.5% of cases of digestive cancer, liver – 54.5%, lung – 64.5%, breast – 61.1%, gynecological – 73.7%, urological 50.0%.

Memory problems, in the terminal phase, occur in patients in 92.6% of cases of digestive cancer, liver – 81.8%, lung – 80.6%, breast – 72.2%, gynecological – 94.7%, urological 85.7%.

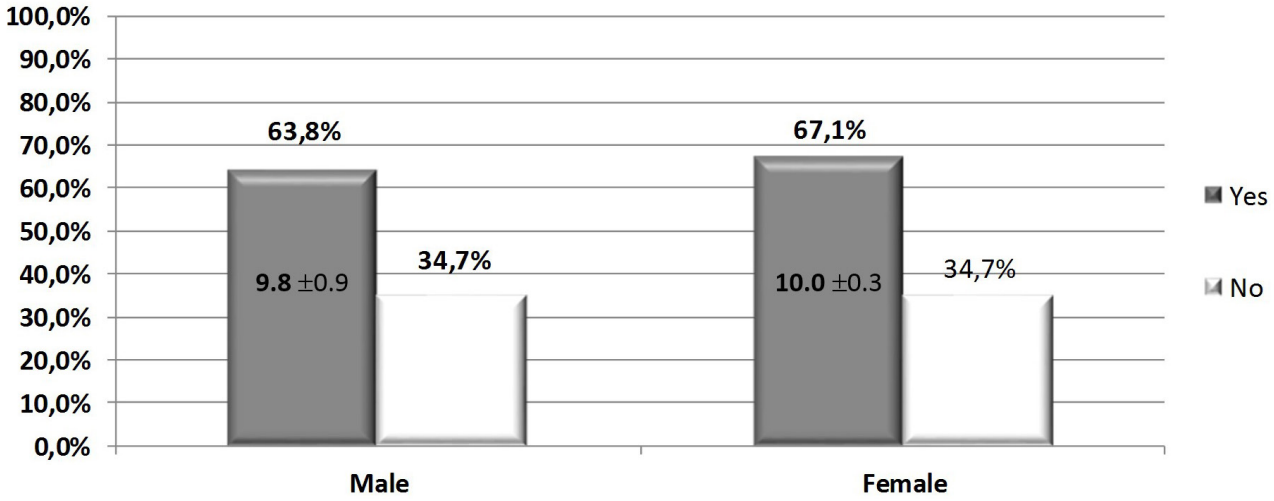
67.3% of terminal oncology patients have vision problems, 66.0% – hearing problems, 73.3% – balance or dizziness problems, 65.3% – mood or personality changes, 83.3%% – memory problems.

Changes in vision occur in 60.0% of male cancer patients and 75.7% of female patients. The difference between the frequencies of this symptom by sex is statistically reliable ($Chi^2 = 2.03$; p = 0.021). Vision changes are observed 2.1 times more frequently in female oncology patients (OR = 0.48, 95% CI OR= = 0.24–0.98).

Balance or dizziness problems occur in 18.8% of men with cancer and 7.1% of women with cancer. The difference between the frequencies of this symptom by sex is not statistically reliable (Chi^2 = =1.59; p = 0.055).

Coma was observed in only 1.3% of terminal oncology patients. According to the primary localization of cancer, coma was observed with the highest incidence (9.1%) during liver cancer.

Figure 3. Frequency of pain syndrome based on the sex of patients in the terminal phase of cancer and the degree of its intensity on a 10-point scale



Source: study findings

Significant and alarming data were observed: on average, 2/3 or more of terminal oncology patients (52% –81% according to localization) regardless of gender, suffer at the end of their lives and die in suffering, with the highest degree of pain intensity (9.4–10.0 points) (p <0.001)!

At the same time, the probability of pain syndrome in digestive cancer is 5.0 times higher than lung cancer (OR = 5.0; 95% CI OR = 1.2–20.0) and 8.3 times higher – compared to gynecological cancer (OR = 8.3; 95% CI OR = 2.2–33.3).

In many patients, in the terminal stage, the pain and suffering caused by the disease cause weakness, although these symptoms can be eased by the use of opioid drugs and psychotropic substances.

According to the WHO, tens of millions of people suffer from excruciating pain, while moderate to severe pain among 5.5 million patients still cannot be managed. More than 80% of cancer patients with advanced forms of the tumor suffer from pain, which is often caused directly by the tumor infiltration. Pain significantly reduces the quality of life and is a clinical indicator of tumor progression. Cancerous pain can be acute or chronic and requires appropriate management.

By introducing the recommendations of world leaders, international organizations, and the World Health Organization (WHO) in pain management, it is possible to solve this problem and control the pain practically 100%, achieving advocacy for many patients in the terminal stage.

A prospective study was conducted in the second phase to evaluate the death mechanisms of patients in the terminal phase of cancer. Through a custom questionnaire, Academician Z. Kakhiani Palliative Care Clinic "RED", 96 patients, in the terminal phase of the disease, were hospitalized in May-June 2021, including 50 oncology (case group) and 44 neurological (control group) patients. A case-control study was conducted.

According to the ECOG status (Figure 169), the majority of patients belonged to the 4th group

(p> 0.005) in both the study (96.0%) and control (97.7%) groups.

Initial localization of cancer were lung (22%), breast (16%), digestive organs (12%), liver and gall-bladder (10%), and gynecological (10%) cancers. All oncology patients (100%) had the 4th clinical stage.

17 oncology patients (34%) underwent radical surgery, 5 underwent non-radical (10%) surgery, and 28 (56%) underwent no surgical treatment.

60% of oncology patients, in the terminal phase, underwent drug therapy, 6% – radiation therapy, and 100% – palliative therapy.

2 tracheostomas, 2 colostomas, 1 nephrostomy, 1 paracentesis were observed in the case group; all 18 stomas were tracheostomas in the control group. χ^2-test = 10.29; p = 0.001

Most of the patients in the study (66.0%) and especially in the control (90.9%) group had a history of HCV (Chi2 = 8.4; p = 0.004), while all patients (100%) were COVID-19 negative in both groups.

The mean body mass index in both cases (14.4) and the control group (15.5) was 3–4 kg less than normal. At the same time the mean BMI was 1 kg less in terminal oncology patients (Z-test = 7.4; p <0.001).

52% of terminal oncology patients had erythrocytopenia, 40% had leukocytopenia, and 38% had thrombocytopenia.

Type 2 diabetes mellitus occurred in only 2% of terminal oncology patients and in 16% of patients in the control group (χ2 = 5.8; p = 0.016).

In the case and control groups, mean blood pressure readings were within the norm.Thereby, both systolic (systolic T / A – Z-test = 5.4; p <0.001) and diastolic (diastolic T / A – Z-test = 4.3; p <0.001) pressure readings were statistically reliable compared to terminal oncological patients in the control group.

Although saturation was lower than normal in both groups, the saturation reading in oncology patients was close to normal (94.2) and statistically reliably higher than the mean of the control group (90.4) (Z = 4.2; p <0.001).

The average length of stay of terminal oncology patients in the palliative clinic was 8.1 days, while the length of stay, in the control group of patients, in the control group was statistically reliably longer (Z = =3.5; p <0.001) and amounted to 19.9 days.

The average respiratory, frequency in terminal oncological patients, was 19.3 per minute, while that of patients in the control group was 19.9 (Z = 2.2; p = 0.030).

18% of terminal oncological patients had normal skin color, anemic – 14%, bluish – 14%, dark brown – 18%, grayish earth – 12%, yellowish – 14%, greenish- 10%.

52% of terminal oncology patients had chilly skin temperature, 32% had normal and only 16% had hot skin temperature, especially on the hands and feet.

Of the 50 terminal oncology patients, 27 (54%) had spontaneous respiration and 23 (46%) had vesicular respiration. In 44 patients, in the control group, similar readings were spontaneous respiration in 41 cases (93.2%) and vesicular respiration in 3 (6.8%). The rate of vesicular respiration was statistically reliably higher in terminal oncology patients (χ^2= 25.0; p <0.001).

Dyspnoea occurred in 42.0% of terminal oncology patients; 14% of them showed dry cough that does not stop; 28.0% had difficulty breathing due to excessive exudate or ascites; 42% had shortness of breath, sometimes prolonged pauses between breaths, noisy breathing with interruptions and anxieties or variable tone of voice; 10% showed cough with bloody and mucous sputum; 28% accumulation of exudate in the pleura; 52% had breathing changes, with mouth breathing becoming irregular and possibly noisy, stopping at some point.

Kussmaul, Biot's, and Grocco's respirations were not observed in any of the terminal oncology patients; in 46% of cases, Cheyenne-Stoke's respiration was observed, and in 44.0% – respiratory arrest was observed.

The following types of respiratory changes were 15 times higher in terminal oncology patients than

in the control group: slowing of breathing, occasional prolongation of pauses between breaths, noisy breathing with interruptions and anxiety, or variable tones (OR = 15.2; 95% CI OR7.).

The risk of accumulation of exudate in the pleura is 17 times lower in terminal oncological patients compared to patients in the control group (OR = 0.06, 95% CI OR = 0.03–0.15).

There was no statistically significant difference between the oncology (52%) and control group (43.2%) of patients in the terminal phase in the frequency of such changes in respiration when the person's breathing becomes irregular and may become noisy and at some point stop – were not observed (OR = 1.42, 95% CI OR = 0.72–2.82).

The risk of chronic cardiovascular failure is 250 times lower in terminal oncology patients than in the control group (OR = 0.004, 95% CI OR = 0.001–0.019).

None of the terminal oncology patients had an acute cardiovascular failure (0%), 6.0% of them showed chronic cardiovascular failure, and 8.0% – syncope.

The majority of terminal oncological patients (98.0%) received food orally, while the majority of patients in the control group (84.1%) – through nasogastric feeding. The probability of oral feeding of terminal oncological patients was 259 times higher than the probability of oral feeding of patients in the control group (OR = 259.0, 95% CI OR = 43.0–1558.0).

Most of the terminal oncology patients had decreased appetite (100.0%), dysphagia (84.0%), weight loss (94.0%), abrupt weight loss, muscle wasting (90.0%), and cachexia (96, 0%).

32.0% of terminal oncology patients complained of nausea and 30.0% of vomiting.

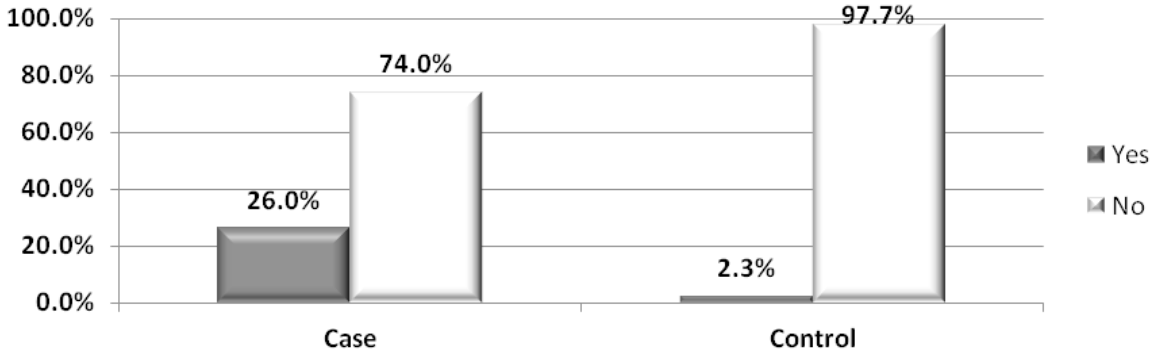
63.3% of terminal oncology patients had constipation, 38.7% – obstruction caused by tumor compression, 28.7% – diarrhea, 46.0% – loss of control over gastric function.

8.0% of terminal oncology patients showed fluid accumulation in the abdomen, 6.0% – fever, and 26% – liver failure.

In both oncological (8.0%) and control group patients (2.3%), in the terminal phase, no statistically significant difference was found between the rates of fluid accumulation in the abdomen (OR = 0.35, 95% CI OR = 0.05–2.65).

26.0% of oncological patients in the terminal phase and 2.3% of patients in the control group showed liver failure. In the terminal phase, the risk of developing liver failure increases 15.1 times in cancer patients (OR = 15.1, 95% CI OR = 2.6–86.6).

Figure 4. Frequency of liver failure in the terminal phase of cancer (case) and diseases of the circulatory system (control)



Source: study findings

Oncology patients received more fluid per day (Z = –6.4, p <0.001), they excreted more fluid through the urine (Z = –6.8, p <0.001) and they accumulated an average of more than 120 ml of fluid per day (Z = –4.5, p <0.001).

2.0% of cancer patients in the terminal phase had urination-related complaints, 32% of them showed a decrease in the amount of urine excreted.

8.0% of oncological patients, in the terminal phase and 2.3% of patients in the control group had renal insufficiency. However, no statistically significant difference was found between the risk of developing renal failure in these groups (OR = 0.4, 95% CI OR = 0.1–2.6).

54.0% of cancer patients in the terminal phase had jaundice of the skin and sclera of the eyes, 42.0% had skin rashes or itching, and 26.0% showed livor mortis.

24 oncological patients in the terminal phase (48.0%) showed metastatic spread of the disease, including 14 (28.0%) – in the bones, 1 (2.0%) in the chest, 2 (4), 0%) – in the abdomen, 3 (6.0%) – in the limbs and 4 (8.0%) – in the lumbar region.

No abnormal bone fractures were observed in 50 terminal oncology patients, 14 patients (28.0%) had metastatic spread of the disease to the bones, accompanied by severe pain.

Terminal oncology patients experience anxiety in 24.0% of cases, delirium in 32.0%, depression in 30.0%, fatigue, exhaustion, impaired physical strength are reported in 90,0%, drowsiness, falling asleep, impaired ability to speak and concentrate in 26.0%.

Terminal oncology patients in 38.0% of cases gradually become less sensitive to touch or sound; 2.0% hear or see people or objects that are not there, they are preparing for their long journey or greeting the dead; 36.0% completely lose consciousness; 44.0% of them are confused and disoriented.

Terminal oncology patients report changes in vision in 8.0% of cases, there are hearing problems in 8.0%, balance or dizziness problems in 48.0%, memory problems in 22.0%, and 8.0% fall into a coma.

Thereby, the severity of coma on the Glasgow scale was higher in control group patients (8.8) compared with terminal oncology patients (13.6) ($Z = -13.69$, $p < 0.001$).

Drowsiness and falling asleep in the terminal phase were observed with equal frequency in both oncology patients (26.0%) and control group (29.5%) (OR = 0.8, 95% CI OR = 0.34–1.80).

Confusion, uncertainty in time, place, and personalities, including family members and close friends, were reported in 22.0% of terminal oncology patients and in 61.4% of control group patients. At the same time, the probability of developing this condition is 5.5 times lower in cancer patients in the terminal phase (OR = 0.18, 95% CI OR = 0.08–0.38).

The tendency for loss of consciousness and recurrence was observed in 6.0% of cases in terminal oncology patients and in 36.4% of control group patients. At the same time, the probability of developing this condition is 9.1 times lower in oncological patients in the terminal phase (OR = =0.11, 95% CI OR = 0.04–0.34).

Complete loss of consciousness was observed in 36.0% of cases in oncological patients and in 68.2% of patients in the control group. At the same time, the probability of developing this condition is 3.8 times less in oncological patients in the terminal phase (OR = 0.26, 95% CI OR = 0.13–0.54).

The tendency for the patient to gradually become less sensitive to touch or sound was observed in 38.0% of terminal oncology patients and in 6.8% of control group patients. At the same time, the probability of developing this condition is 8.4 times higher in cancer patients in the terminal phase (OR = =8.4, 95% CI 2.8–25.0).

Confusion and disorientation were observed in 44.0% of cases in terminal oncology patients and in 68.2% of control group patients. Thereby, the probability of developing this condition is 2.7 times less in oncological patients in the terminal phase (OR = 0.37, 95% CI OR = 0.18–0.75).

Hearing problems were observed in 8.0% of terminal oncology patients and in 2.3% of control group patients. However, no statistically significant difference was found between the groups studied in

terms of hearing problems (OR = 3.74, 95% CI OR= = 0.58–24.3).

Memory problems were reported in 22.0% of terminal oncology patients and in 4.5% of control group patients. Thereby, the probability of memory problems is 5.9 times higher in oncological patients in the terminal phase (OR = 5.9, 95% CI OR = 1.59–22.1).

The incidence of pain syndrome in terminal oncology patients was 68.0% and the pain intensity was 8.4 points. Meaning that 2/3 of the oncology patients in the terminal phase died suffering from unbearable, severe pain at 8.4 points.

Key Findings:

1. Changes in skin color (anemic), lowering of body temperature, dropping of blood pressure, slowing of lymph and blood circulation, decreased saturation, fluid retention in the body (especially in the lower extremities), ascites, accumulation of exudate in the pleural cavity, renal failure, cachexia, gastric activity loss, dyspnea, syncope are most likely common accompanying processes of thanatogenesis.

2. The specific mechanisms of current death in cancer progression and terminal phase are tumor intoxication, liver failure, compression and infiltration of the urinary tract (bladder or urinary tract) or digestive tract (intestine), and development of uremia and obstruction related to them, permanent pain syndrome.

3. In the terminal phase, permanent pain syndrome in 2/3 of cases is a mix of specific symptoms characteristic of cancer, in which the psychoemotional and mental feelings of patients are involved along with the unbearable physical suffering and pain.

Practical recommendations:

1. A further study of the possible impact of the COVID-19 pandemic on structural changes in cancer death is recommended.

2. In 2/3 of the patients in the terminal stage, severe pain is still not managed! In order to ease the suffering of patients with severe pain, to delay the progression of the disease, to increase life expectancy and quality, and therefore to advocate for cancer control, it is recommended to use an increased dose of opioid medications and psychotropic substances in the management of pain syndrome.

3. By introducing the recommendations of world leaders, international organizations, and the World Health Organization (WHO, Geneva, 2018) in pain management, it is possible to solve this problem and control the pain practically 100%, achieving advocacy for many patients in the terminal stage.

4. In the terminal stage of cancer, for further, in-depth study of the mechanisms of death, it is recommended to conduct additional studies in the field of thanatology.

5. For cancer control advocacy, it is recommended to prepare follow-up services for oncology patients (screening-diagnostic, treatment-rehabilitation, care, pain syndrome cessation), especially the preparation of guidelines for delivery with private and state programs and state programs during ECOG4 (thanatological service). Providing packages for each patient to receive appropriate service at each stage.

6. It is recommended that the issue of pain syndrome cupping be included in the Annual Cancer Control Report (NCDC). The purpose of the annual monitoring is to achieve a 100% reduction in the permanent pain syndrome.

References:

1. American Cancer Society: Cancer Facts and Figures 2019. Atlanta, Ga: American Cancer Society, 2019. Available onlineExit Disclaimer. Last accessed June 7, 2019.
2. American Cancer Society (2019). Facts & Figures 2019: US Cancer Death Rate has Dropped 27% in 25 Years. Cancer Statistics 2019, Jan 8, 2019. https://www.cancer.org/latest-news/facts-and-figures-2019.html
3. Anna Azvolinsky (2015). 8 Signs Death Is Imminent in Advanced Cancer Patients. End-of-Life Care. February 9, 2015. https://www.cancernetwork.com/end-life-care/8-signs-death-imminent-advanced-cancer-patients
4. ASCO (2019). Care through the Final Days. ASCO Journals, Approved by the Cancer.Net Editorial Board, 05/2019. https://www.cancer.net/navigating-cancer-care/advanced-cancer/care-through-final-days
5. Ben-Aharon I., Gafter-Gvili A., Paul M., et al.: Interventions for alleviating cancer-related dyspnea: a systematic review. J Clin Oncol 26 (14): 2396–404, 2008. [PUBMED Abstract]
6. Bray F., Colombet M., Mery L., Piñeros M., Znaor A., Zanetti R. and Ferlay J., editors (2017) Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr, accessed [date]. The printed version of this volume (IARC Scientific Publication No. 166) will be available for download in PDF format at the IARC Publications website (http://publications.iarc.fr/) in 2019.http://ci5.iarc.fr/CI5-XI/Default.aspx
7. Bokhman J. V. Gynecological Oncology Guide (in Russian) // Leningrad: Medicine.–1989.– 464 P.
8. Bokhman J. V. Uterine Cancer (in Russian) // Kishenov: Stinitsca –1972. – 220 P.
9. Bokhman J. V. Uterine cancer metastases (in Russian) // Leningrad: Medicine. – 1976. – 160 P.
10. Breitbart W, Gibson C, Tremblay A: The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 43 (3): 183–94, 2002 May-Jun. [PUBMED Abstract]
11. Bruera E., Bush S.H., Willey J., et al.: Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer 115 (9): 2004–12, 2009. [PUBMED Abstract]
12. Bruera E., Schmitz B., Pither J., et al.: The frequency and correlates of dyspnea in patients with advanced cancer. J Pain Symptom Manage 19 (5): 357–62, 2000. [PUBMED Abstract]
13. Campbell M.L. Psychometric testing of a respiratory distress observation scale. J Palliat Med 11 (1): 44–50, 2008 Jan-Feb. [PUBMED Abstract]
14. Cancer Research UK (2019). The last few weeks and days. Final days. Last reviewed: 21 Feb 2019. https://www.cancerresearchuk.org/about-cancer/coping/dying-with-cancer/last-few-weeks-and-days/final-days
15. Callanan M., Kelley P. Final Gifts: Understanding the Special Awareness, Needs, and Communications of the Dying. New York, NY: Poseidon Press, 1992.
16. Centeno C., Sanz A., Bruera E. Delirium in advanced cancer patients. Palliat Med 18 (3): 184–94, 2004. [PUBMED Abstract]
17. Christopher P. Wild, Elisabeth Weiderpass, and Bernard W. Stewart, editors (2019). World Cancer Report. Cancer research for cancer prevention. WHO, Geneva, 2019. https://www.iarc.fr/cards_page/world-cancer-report

18. Coyle N., Adelhardt J., Foley K.M., et al.: Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. J Pain Symptom Manage 5 (2): 83–93, 1990. [PUBMED Abstract]
19. Dong S.T., Butow P.N., Costa D.S., et al.: Symptom clusters in patients with advanced cancer: a systematic review of observational studies. J Pain Symptom Manage 48 (3): 411–50, 2014. [PUBMED Abstract]
20. Goodman D.C., Fisher E.S., Chang C.H., et al.: Quality of End-of-Life Cancer Care for Medicare Beneficiaries: Regional and Hospital-Specific Analyses. Lebanon, NH: Dartmouth Institute for Health Policy & Clinical Practice, 2010. Available onlineExit Disclaimer. Last accessed March 1, 2019.
21. Hui D., dos Santos R., Chisholm G.B., et al.: Symptom Expression in the Last Seven Days of Life Among Cancer Patients Admitted to Acute Palliative Care Units. J Pain Symptom Manage 50 (4): 488–94, 2015. [PUBMED Abstract]
22. Hui D., dos Santos R., Chisholm G., et al.: Clinical signs of impending death in cancer patients. Oncologist 19 (6): 681–7, 2014. [PUBMED Abstract]
23. Hui D., Morgado M., Vidal M., et al.: Dyspnea in hospitalized advanced cancer patients: subjective and physiologic correlates. J Palliat Med 16 (3): 274–80, 2013. [PUBMED Abstract]
24. Janet Colwell (2014). ASCO: Smart Technology Monitoring System Improves Care at End of Life. End-of-Life Care, October 23, 2014. https://www.cancernetwork.com/end-life-care
25. Jennifer Berry (2018). End-of-life symptoms of metastatic breast cancer. Medical News Today, 27 November 2018. https://www.medicalnewstoday.com/articles/323824.php
26. Kåss R.M., Ellershaw J: Respiratory tract secretions in the dying patient: a retrospective study. J Pain Symptom Manage 26 (4): 897–902, 2003. [PUBMED Abstract]
27. Leah Lawrence (2017). Early Palliative Care Decreased Healthcare Use at End of Life. End-life-care. August 23, 2017. https://www.cancernetwork.com/end-life-care
28. Lawlor P.G., Gagnon B., Mancini I.L., et al.: Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 160 (6): 786–94, 2000. [PUBMED Abstract]
29. Lindsey A. Torre, Rebecca L. Siegel, Elizabeth M. Ward and Ahmedin Jemal (2016). Global Cancer Incidence and Mortality Rates and Trends – An Update. PubMed: Cancer Epidemiol Biomarkers Prev; 25(1); 16–27. ©2015 AACR.DOI: 10.1158/1055–9965.EPI-15–0578 Published January 2016. http://cebp.aacrjournals.org/content/25/1/16
30. Lokker M.E., van Zuylen L., van der Rijt C.C., et al.: Prevalence, impact, and treatment of death rattle: a systematic review. J Pain Symptom Manage 47 (1): 105–22, 2014. [PUBMED Abstract]
31. McGrath P., Leahy M.: Catastrophic bleeds during end-of-life care in haematology: controversies from Australian research. Support Care Cancer 17 (5): 527–37, 2009. [PUBMED Abstract]
32. Morris J.N., Suissa S, Sherwood S, Wright SM, Greer D. Last days: a study of the quality of life of terminally ill cancer patients.J Chronic Dis. 1986;39(1):47–62.PMID:2418050[Indexed for MEDLINE] https://www.ncbi.nlm.nih.gov/pubmed/2418050
33. Morita T., Takigawa C., Onishi H., et al.: Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial. J Pain Symptom Manage 30 (1): 96–103, 2005. [PUBMED Abstract]
34. Mercadante S., Villari P., Fulfaro F: Gabapentin for opiod-related myoclonus in cancer patients. Support Care Cancer 9 (3): 205–6, 2001. [PUBMED Abstract]
35. Maltoni M., Scarpi E., Rosati M., et al.: Palliative sedation in end-of-life care and survival: a systematic review. J Clin Oncol 30 (12): 1378–83, 2012. [PUBMED Abstract]

36. Nancy E. Morden, Chiang-Hua Chang, Joseph O. Jacobson, Ethan M. Berke, Julie P. W. Bynum, Kimberly M. Murray, David C. Goodman (2012). End-Of-Life Care For Medicare Beneficiaries With Cancer Is Highly Intensive Overall And Varies Widely. Health Aff (Millwood). 2012 Apr; 31(4): 786–796.doi: 10.1377/hlthaff.2011.0650. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3338099/
37. Sykes N., Thorns A. The use of opioids and sedatives at the end of life. Lancet Oncol 4 (5): 312–8, 2003. [PUBMED Abstract]
38. Tishelman C., Petersson L.M., Degner L.F., et al.: Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. J Clin Oncol 25 (34): 5381–9, 2007. [PUBMED Abstract]
39. Thorns A., Sykes N. Opioid use in last week of life and implications for end-of-life decision-making. Lancet 356 (9227): 398–9, 2000. [PUBMED Abstract]
40. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. WHO, Geneva, 2018, 138 p.
41. Wright A.A., Zhang B., Ray A., et al.: Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 300 (14): 1665–73, 2008. [PUBMED Abstract]
42. Wright A.A., Keating N.L., Balboni T.A., et al. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. J Clin Oncol 28 (29): 4457–64, 2010. [PUBMED Abstract]
43. Wee B., Browning J., Adams A., et al.: Management of chronic cough in patients receiving palliative care: review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland. Palliat Med 26 (6): 780–7, 2012. [PUBMED Abstract]
44. Wildiers H., Menten J. Death rattle: prevalence, prevention and treatment. J Pain Symptom Manage 23 (4): 310–7, 2002. [PUBMED Abstract]

Contents