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The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

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ABOUT THE JOURNAL

Scientific Reports in Medicine is a scientific publication of Academician Publishing and published three times a year online.

It is an open access scientific journal, which publishes original contributions in medical disciplines pertaining to human medicine. In this context, the Journal publishes original researches, case reports, and reviews based on clinical and experimental studies in all areas of human medicine. It is a scientific, periodic journal based on the principles of blind peer-review process. The publication language is English. The Journal is published online three times a year on April, August, and December.

Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts submitted to the Journal are screened in terms of originality.

All manuscripts should be submitted by online system of the Journal.

The Journal aims to;

- Publish original contributions from different scientific disciplines through the advisory board covering a wide range of medical disciplines,
- Offer all its content freely available without charge to the user or his/her institution, to make research freely available to the public, and to support a greater global exchange of knowledge,
- By permitting authors to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), to lead productive exchanges, as well as earlier and greater citation of published work.

Subject areas include, (but are not restricted) to the clinical and experimental studies of the following fields:

- First Aid and Emergency Medicine
- Family Medicine
- Public Health and Preventive Medicine
- Internal Diseases
- General Surgery
- Gynecology and Obstetrics
- Ear, Nose and Throat Diseases
- Eye Diseases
- Orthopedics and Traumatology
- Radiology and Radiodiagnostics
- Anesthesia and Intensive Care Medicine

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- Adolescent Diseases
- Childhood Diseases
- Multisystem Diseases
- Physical Medicine and Rehabilitation
- Forensic Medicine
- Mental Health and Diseases
- Cardiovascular System Diseases
- Nervous System Diseases
- Neurosurgery
- Respiratory System Diseases
- Infectious Diseases
- Occupational Diseases
- Nuclear Medicine
- Oncological Diseases
- Sports Medicine
- Genetic Diseases
- Medical Pathology

The journal covers all relevant branches in human medicine specialties of the topics mentioned above.

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AUTHOR GUIDELINES

Thank you for your interest in submitting your manuscript to Scientific Reports in Medicine for editing and publication consideration. In order to facilitate preparation and submission of your manuscript, we have prepared this guideline explaining basic points that should be taken into account when preparing the paper.

Scientific Reports in Medicine is a scientific publication of Academician Publishing and published three times a year online.

It is an open access scientific journal, which publishes original contributions in medical disciplines pertaining to human medicine. In this context, the Journal publishes original researches, case reports, and reviews based on clinical and experimental studies in all areas of human medicine. It is a scientific, periodic journal based on the principles of blind peer-review process. The publication language is English. The Journal is published online three times a year on April, August, and December.

Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts submitted to the Journal are screened in terms of originality.

All manuscripts should be submitted by online system of the Journal.

Subject areas include, but are not restricted to the clinical and experimental studies of the following fields: first aid and emergency medicine, family medicine, public health and preventive medicine, internal diseases, general surgery, gynecology and obstetrics, ear, nose and throat diseases, eye diseases, orthopedics and traumatology, radiology and radiodiagnostics, anesthesia and intensive care medicine, adolescent diseases, childhood diseases, multisystem diseases, physical medicine and rehabilitation, forensic medicine, mental health and diseases, cardiovascular system diseases, nervous system diseases, neurosurgery, respiratory system diseases, infectious diseases, occupational diseases, nuclear medicine, oncological diseases, sports medicine, genetic diseases, medical pathology.

The journal covers all relevant branches in human medicine specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Manuscript Preparation

All manuscripts which will be published in the journal must be in accordance with research and publication ethics. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees.

Process of Peer Review

The journal utilizes a standard online site (SRINMED), operated by Academician Publishing, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration

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of publication to the journal, the journal manager and editorial staff review the submission to assure all required components as outlined in this Guide for Authors are included. The manuscript is then assigned to one of the co-editors (either the editor in chief or an associate editor) who directs and oversees the peer-review process. The co-editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

About the scientific language to be used in writing your manuscript

In line with the recommendation of the international directories we applied to increase the scientific effectiveness of our journal and enrich its content, our Editorial Board has decided that the studies to be published in English. So the manuscripts sent to our journal are subject to English language control and revision.

Our experience from previous articles has shown that most of the articles prepared in English need to be improved in terms of fluent readability and intelligibility, as well as scientific and technical examination. Most of the manuscrpits should undergo a comprehensive review and revision process in terms of language, before they were included in the review stage.

Therefore, we recommend that you receive professional English editing and proofreading services before submitting your manuscript to our journal, although it is not mandatory.

You can contact Academician Publishing to receive Editing and Proofreading services for a fee. You can click here to contact Academician Publishing.

Our journal does not have any commercial partnership with any translation or proofreading service company, and our authors are absolutely free to make their choices as they wish.

By uploading the revised English full text of your manuscript to our Journal system by ensuring that English Editing and Proofreading is carried out by a local or foreign professional, you may minimize the possibility of rejection due to translation errors.

Use of first person

In addition, it is necessary to make the necessary checks and revisions in terms of language of your work and to ensure integrity in terms of language and time use throughout the entire article.

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Expressions such as ... "Our study, in our study, we, we did, we found, we aimed, I did, I found, I think ... etc." should be revised as follows;

• In this study, … it was found/determined/… or

• In this study … it was aimed to …

Names made up of single word should not be abbreviated.

Instead of,
• Hypertension (HT) is one of the most …

Throughout the manuscript, you should use;

• Hypertension is one of the most …

Instead of,

• Rituximab (RTX) is an IgG1 kappa chimeric monoclonal

Throughout the manuscript, you should use;

• Rituximab is an …

Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)

For example;

• In 2 studies, …

Should be replaced with;

• In two studies …

For example;

• … perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,

Should be replaced with;

• … perivascular lymphotic infiltration in only 10% of patients … in 7% of patients …

Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.

• determined to be high

Should be replaced with;

• … was found to be high.

Or throughout the entire manuscript;

• found to be significantly higher …

If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "… a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.

• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).

Should be replaced with;

While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Methods, Results [Findings], and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection

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of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

Sections

Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Please, do not cite figures, tables or references in the abstract.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. All the articles submitted to the journal require to include abstract in English. Abstracts of original articles should not exceed 250 words.

Keywords

Three to six words or determinative groups of words should be written below the abstract. Abbreviations should not be used as keywords. Keywords in English should be chosen from MESH (Medical Subject Headings http://www.nlm.nih.gov/mesh) index. Abbreviations cannot be used as keywords, but instead they should be written explicitly. Letters that do not exist in Latin alphabet (e.g. alpha, beta, delta etc.) should be used with their pronunciation.

Examples; carbon monoxide, firearms, sexual abuse, oral mucosa

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results.

The authors should clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), autopsied persons, including eligibility and exclusion criteria and a description of the source population.

In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results [Findings] section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee

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is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential.

Informed consent should be obtained in human studies and it should be stated in the manuscript.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

The authors should describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. They should define statistical terms, abbreviations, symbols and should specify the statistical software package(s) and versions used.

Results [Findings]

You should present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Please, do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

You should give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. You should restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Please, use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Discussion

It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results [Findings] section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote

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self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Laws (e.g., penal code), statutes and regulations are not scientific writings. In addition to being published on the official gazette, since it is published on various internet sites, a reference number should not be given to laws, statutes and regulations. If it is to be cited within the text, the law could be cited by specifying the number of the law, the date and number of publications in the official gazette (e.g., A Review of Article 5 of the Turkish Criminal Penal Code No. 5237). They should not be numbered within the text, or in the reference list.

To minimize citation errors, references can be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. References should be numbered consecutively in the order in which they are first mentioned in the text. Roman numerals should be avoided. Identify references in text, tables, and legends by Arabic numerals (1, 2, 3 … 9, 0) in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

If you refer to a work more than once, use the first number also for the second and following references. References to more than one source in the same phrase may be entered like this: (2-4), i.e., references 2 through 4 in the reference list, and (2-4, 8), i.e. the references 2 through 4, plus reference no 8 in the list of references.

Sample for in-text citation:

In a clinical research in healthy individuals, Ellis (25) has studied the sciatic nerve excursion using ultrasound technique.
Wright and Ellis (10) has investigated the excursion of nerves around the elbow joint.
In another and similar cadaveric study by Wright et al (13), the radial nerve median excursion values were 4.1, 8.8, and 0.2, 0.1 mm with motions of shoulder, elbow, wrist and fingers respectively.

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4). Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

The Vancouver system, also known as Vancouver reference style or the author–number system, is a citation style that uses numbers within the text that refer to numbered entries in the reference list. Vancouver style is used by MEDLINE and PubMed. The names "Vancouver system" or "Vancouver style" have existed since 1978. The latest version of the latter is Citing Medicine, per the References > Style and Format section of the ICMJE Recommendations. In 1978, a committee of editors from various medical journals, the International Committee of Medical Journal Editors (ICMJE), met in Vancouver, BC, Canada to agree to a unified set of requirements for the articles of such journals. This meeting led to the establishment of the Uniform Requirements for Manuscripts

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Submitted to Biomedical Journals (URMs). Part of the URMs is the reference style, for which the ICMJE selected the long-established author–number principle.

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine, its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

Scientific Reports in Medicine, since the first day of its publication uses the PubMed/NLM reference style. Thus, references should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles web page and detailed in the NLM's Citing Medicine, 2nd edition.

According to the Vancouver rules, you can only refer to the literature you have read yourself. If you find anything interesting in a text where it is referred to another text, you must read and refer to the original.

Reference List

The reference list should be ordered numerically in the order in which the references appear in the text.
The journal's name may be abbreviated, according to the abbreviation rules for journal titles. Records retrieved from a search for the full journal title in the National Library of Medicine's search page include the abbreviated title.

Authors' names should be given as surname followed by initials. There should be a space between surname and initials. A maximum of two initials are allowed for each author, they should be entered without spaces or punctuation. Different authors should be separated by a space and a comma. A period (.) should follow the last author's name. If six or more authors, list the first six authors followed by et al.

Only capital letter of the first word of the title, proper nouns, proper adjectives, acronyms, and initialisms should be capitalized.

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Scientific Reports in Medicine, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal.

With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

Note: Please, do not insert Pubmed ID (PMID) or Pubmed Central ID (PMCID) records to the reference list since they are useless in determining the citation counts.

We place great importance to the addition of DOIs to the references.

Sample for Journal Article without DOI

Dokgöz H, Kar H, Bilgin NG, Toros F. Forensic Approach to Teenage Mothers Concept: 3 Case Reports. Turkiye Klinikleri J Foren Med 2008;5(2):80-4

Kaufman DM, Mann KV, Miujtjens AM, Van der Vleuten CP. A comparison of standard setting procedures for an OSCE in undergraduate medical education. Academic Medicine 2000;75:267–71.

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Sample for Journal Article with DOI

Koçak U, Alpaslan AH, Yağan M, Özer E. Suicide by Homemade Hydrogen Sulfide in Turkey a Case Report. Bull Leg Med. 2016;21(3):189-192. https://doi.org/10.17986/blm.2016323754

Article not in English

Kar H, Dokgöz H, Gamsız Bilgin N, Albayrak B, Kaya Tİ. Lazer Epilasyona Bağlı Cilt Lezyonlarının Malpraktis Açısından Değerlendirilmesi. Bull Leg Med. 2016;21(3):153-158. https://doi.org/10.17986/blm.2016323748

Books and Other Monographs

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113

Emmerson BT. Gout and renal disease. In: Massry SG, Glassock RJ (Editors). Textbook of Nephrology 1. Baskı, Baltimore: Williams and Wilkins; 1989. p. 756–760.

Conference proceedings

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Article published on the Internet ahead of the print version:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Part of a homepage/Web site [Edited 28 Dec 2016]

American Medical Association [Internet]. Chicago: The Association; c1995-2016 [cited 2016 Dec 27]. Office of International Medicine; [about 2 screens]. Available from: https://www.ama-assn.org/about/office-international-medicine

Thesis

Skrtic L. Hydrogen sulfide, oil and gas, and people's health [Master's of Science Thesis]. Berkeley, CA: University of California; 2006.

Weisbaum LD. Human sexuality of children and adolescents: a comprehensive training guide for social work professionals [master's thesis]. Long Beach (CA): California State University; 2005. 200 p.

For the reference types not listed here, please visit Samples of Formatted References for Authors of Journal Articles available at Medline Web site (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

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It would be appropriate to place the tables at the end of the main text. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text. Give each column a short or an abbreviated heading. In the tables, case counts (n) and percentages (%) should be specified in separate columns, not in the same cell.

Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes and use symbols to explain information if needed. Symbols may be as alphabet letters or such symbols as *, p t> T §). Please, identify statistical measures of variations, such as standard deviation and standard error of the mean.

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural. While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

In the ancient times when digital cameras have not been invented, the photos taken by analogue cameras were used to be printed on photo papers. In order to transfer these photos to the digital environment, they had to be scanned by optical devices called scanners. On the same dates, desktop publishing and printing technology was far beyond the digital photography, and many years had passed since the invention of laser printing technology. Here, several technical terms should be explained to make the concept clearer. DPI is used to describe the resolution number of dots per inch in a digital print and the printing resolution of a hard copy print dot gain, which is the increase in the size of the halftone dots during printing. A dot matrix printer, for example, applies ink via tiny rods striking an ink ribbon, and has a relatively low resolution, typically in the range of 60 to 90 DPI (420 to 280 μm). An inkjet printer sprays ink through tiny nozzles and is typically capable of 300–720 DPI. A laser printer applies toner through a controlled electrostatic charge and may be in the range of 600 to 2,400 DPI. Along with the cheaper memory chips, 1200 dpi printers have been widely available in the consumer market since 2008. Monitors do not have dots but do have pixels. The closely related concept for monitors and images is pixels per inch or PPI. Old CRT type video displays were almost universally rated in dot pitch, which refers to the spacing between the subpixel red, green and blue dots which made up the pixels themselves. The DP measurement of a printer often needs to be considerably higher than the pixels per inch (PPI) measurement of a video display in order to produce similar-quality output. This dithered printing process could require a region of four to six dots (measured across each side) in order to faithfully reproduce the color in a single pixel. An image that is 100 pixels wide may need to be 400 to 600 dots in width in the printed output; if a 100×100-pixel image is to be printed in a one-inch square; the printer must be capable of 400 to 600 dots per inch to reproduce the image. The dpi of early model laser printers was 300 to 360, thus scanning images at 300 DPI was a common practice at that time.

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is

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to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

Therefore, an image that is 2048 pixels in width and 1536 pixels in height has a total of 2048×1536 = 3,145,728 pixels or 3.1 megapixels. One could refer to it as 2048 by 1536 or a 3.1-megapixel image. Or, you can think of it as a very low-quality image (72 ppi) if printed at about 28.5 inches wide, or a very good quality (300 ppi) image if printed at about 7 inches wide.

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 μm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

In computing, an image scanner—often abbreviated to just scanner, is a device that optically scans images, printed text, handwriting or an object and converts it to a digital image. Although the history of digital cameras dates back to the 1970s, they have become widely used in the 2000s. While the resolution of the first digital camera invented by Kodak was as low as 100 by 100 pixels (0.01 megapixels), the first commercially available digital camera, Fujix DS-1P had a resolution of 0.4 megapixels. On the other hand, modern scanners are considered the successors of early telephotography and fax input devices. The pantelegraph was an early form of facsimile machine transmitting over normal telegraph lines developed by Giovanni Caselli, used commercially in the 1860s, that was the first such device to enter practical service. The history of the first image scanner developed for use with a computer goes back to 1957. Color scanners typically read RGB (red-green-blue color) data from the array. This data is then processed with some proprietary algorithm to correct for different exposure conditions and sent to the computer via the device's input/output interface. Color depth varies depending on the scanning array characteristics but is usually at least 24 bits. High quality models have 36-48 bits of color depth. Another qualifying parameter for a scanner is its optical resolution, measured in pixels per inch (ppi), sometimes more accurately referred to as samples per inch (spi).

Images in web pages, video, and slide shows can be as low as 72 PPI for a static image or 150 PPI if we are going to focus in on the image. For printing, the DPI needs to be larger, with images scanned in at least 300 DPI. The DPI standard for and images to be printed within journals and books is 300 DPI and for museum exhibits, it's 600 DPI.

The most important factors determining image quality of digital images can be considered as pixel dimensions and color depth. Increasing the dpi value of an image by resampling in Photo Editors (e.g., Adobe Photoshop) has no

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improving effect on its quality, but it lets us to determine target printing size.

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

Long story short, it is not technically possible to talk about DPI value for images that were taken by digital cameras or any type of digital images that were transferred to the computer's storage media. The DPI value stored within exif information of images is just a virtual value just to guide the photo editing software and the graphic artist to determine the target printing size of that image.

Requirements for Digital Media

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Due to the reasons explained above, images should be taken by a digital camera of 5 megapixels or more in JPEG, RAW, or TIFF format, and should be inserted in their original form as JPEG or TIFF files.

Paper-printed images or documents should be scanned at 300 DPI resolution and should be inserted as TIFF or JPEG files.

Each vector graphic software has its own built-in settings and may have been preset at 72 dpi. So, the document should be created enough big to obtain the image in the desired dimensions. The vector graphics should be exported to a rasterized image format and inserted such as JPEG or TIFF files.

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The manuscript could be of up to 2000 words (excluding references and abstract) and could be supported with up to 25 references. Care should be taken to ensure that the number of figures or tables does not exceed 5-6 each.

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EDITORIAL

The final stage of a scientific research process is to share findings to the public and the scientific community, in other words, publishing. We are aware of the importance and challenges of this stage. Gerard Piel's statement, "Science without publication is dead," effectively summarizes the significance of this matter. When defining the mechanism that creates a scientific article, a valid publication is only possible if it undergoes an objective evaluation process. A fundamental, acceptable scientific publication should be the initial explanation that contains sufficient information, enabling peers to evaluate observations, replicate experiments, and assess intellectual processes. As the journal Scientific Reports in Medicine (SRINMED), we are excited to share the thrill of launching our publication journey with our first issue, and we are pleased to share it with you, esteemed science readers. I would like to thank all the authors who contributed to our first issue.

Güzel and colleagues shared the relationship between liver damage and risk factors in COVID-19 patients in their article titled "Hepatotoxicity and Its Impact on Mortality in COVID-19 Patients." Candevir and colleagues presented the rates and characteristics of central line associated bloodstream infections in intensive care units in their article titled "Central Line Associated Bloodstream Infections Outside the Intensive Care Unit: A 2-Year Analysis." Dağlı and colleagues discussed the factors influencing health literacy levels among healthcare workers in their article titled "Evaluation of Occupational Health Literacy of Health Workers in Adana, Turkey." Pazarcı explained the molecular foundations of memory and learning in his review titled "Molecular Basis of Learning and Memory." Camadan summarized current treatments in small cell lung cancer in his review titled "Current Developments in Small Cell Lung Cancer."

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RESEARCH ARTICLE

Hepatotoxicity and Its Impact on Mortality in COVID-19 Patients*

Hepatotoxicty in COVID-19

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Abstract:

Objective: **"**COVID-19 related liver damage" can occur frequently in course of COVID-19 disease and cause significant problems. Our research aims to identify the risk factors for liver damage seen in COVID-19 cases and explore the connection between liver damage, illness course, and death.

Method: One hundred adult patients treated in the hospital between 01.08.2021-01.03.2022 were included in the study. Impaired liver function tests were identified as having alanine aminotransferase and aspartate aminotransferase levels exceeding upper laboratory limits.

Results: The mean age of patients included in study was 57.9 ± 14.9 years, with 49% of them being male. In our study, we had an 8% death rate and 37% of patients had abnormal liver function tests. The presence of severe disease ($p<0.001$), anorexia symptoms ($p=0.027$), and abdominal pain ($p=0.010$) were significant for mortality. A prolonged hospital stay was significantly associated with death ($p=0.029$), with the mean length of hospital stay being 11.8 ± 4.6 days. Favipiravir use for longer than five days was associated with a substantial risk of liver damage ($p=0.044$) and mortality ($p=0.020$), while use of antibiotics in carbapenem group was associated with a significant risk of death ($p=0.001$).

Conclusions: It should be noted that an increase in liver tests may be observed in a significant portion of COVID-19 patients, and in some of these patients, this may be a sign of disease progression and mortality.:

Keywords: COVID-19, liver function tests, mortality, alanine aminotransferase, aspartate aminotransferase

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INTRODUCTION

Coronavirus disease 2019 (COVID-19); It has become an epidemic that has spread rapidly around the world since the first months of 2020, causing disruption among human communities and significant economic instability, and has opened a new perspective on respiratory infections. Although the rate of spread of the disease has decreased under current conditions, the situation continues dynamically, especially in the winter months, and epidemiological data change from day to day. According to WHO data dated February 3, 2024, the total number of confirmed cases was approximately 773 million, while 6.98 million people died due to this disease (1). From the beginning of COVID-19 until the present, a number of research have demonstrated that the virus affects not only the respiratory system but also the neurological, cardiovascular, and gastrointestinal systems (2). Numerous people, particularly those with severe or critical illnesses, have been shown to have liver damage, or hepatotoxicity, according to studies (3). The majority of COVID-19 patients with liver dysfunction were found to be male, older, and to have a higher body mass index (4). According to reports, liver dysfunction lengthens hospital stays, worsens prognoses, and raises the likelihood of a severe COVID-19 infection. (3, 4). Our hypothesis for this study was that COVID-19-related inflammation and severe sickness damage numerous organs, including the liver, and have a direct impact on the disease's progression. It was believed that defining risk factors for liver injury in COVID-19, endorsing related research, and forging a shared understanding of the care and treatment of these patients could add something to the body of literature. Finding the risk factors for hepatotoxicity associated with COVID-19, investigating the association between hepatotoxicity and mortality, and investigating the relationship between COVID-19 and liver malfunction or hepatotoxicity were the main goals of the study.

METHODS

Study Design

Our single-center and descriptive study was conducted based on retrospective data. It was carried out between 01.08.2021 and 01.03.2022, based on the findings of patients hospitalized in the ward and intensive care unit (ICU) where COVID-19 patients were followed in a tertiary hospital. On March 4, 2022, Cukurova University's non-interventional clinical research ethics committee granted the study approval (No. 48/120). The hospital's ethical guidelines, the national research committee's guidelines, and the 1964 Declaration of Helsinki were followed in every procedure carried out during the study involving human subjects.

Participants

100 patients aged 18 and over, whose COVID-19 infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) results from nasal and pharyngeal swab samples, were included in the study. Patients were divided into those with and without liver damage. Initially, 164 patients were determined for the study, but later 64 patients (16 people with radiological COVID-19 RT-PCR negativity, 28 people with missing laboratory tests, 20 people who did not want to participate in the study) were excluded from the study. According to discharge status, they were divided into two different groups as survivors and deceased patients. The patients' sociodemographic and clinical data, laboratory parameters, radiological findings, and treatments they received during their stay (anticoagulant, antiviral, antibacterial, corticosteroid and anticytokine drugs) were recorded.

Figure 1. Liver Damage Mechanisms Associated with COVID-19

Variables

Comorbidities were categorized according to the Charlson Comorbidity Index as "0 points low, 1-2 points moderate, 3-4 points high, and 5 points and above very high risk". According to the clinical and radiological results of the patients at the time of admission, the severity of the COVID-19 disease was classified into three categories: Those with oxygen saturation above 94% on room air and radiological lung involvement below 25% have mild disease, those with oxygen saturation between 88-94% and radiological lung involvement between 25-49% have moderate disease, those with oxygen saturation below 88% and radiological lung involvement have moderate disease. Those with 50% and above were defined as severe disease. The laboratory range for alanine aminotransferase (ALT) was (10-40 IU/L) and the laboratory range for aspartate aminotransferase (AST) was (15-45 IU/L), and values above these values were recorded as liver damage (hepatotoxicity). Increases in gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels were not considered as primary liver dysfunction. Favipiravir was used as antiviral treatment in all patients (in line with the recommendations of the Ministry of Health COVID-19 monitoring and treatment application guide).

Statistical Analysis

The data were statistically analyzed using IBM SPSS Statistics Version 20.0 package program (Armonk, NY: IBM Corp.). In the investigations, categorical variables were compared using the chi-square test or the Fisher exact test, and the Kolmogorov-Smirnov method was employed to ascertain whether the distribution of the variables was within the normal range. A p-value of less than 0.05 indicated statistical significance.

RESULTS

The study's 49% of patients were men, with an average age of 57.85 ± 14.87 (min.24–max.95). Hepatotoxicity was detected in 37% of the patients, and 8 patients died. At admission, loss of appetite was the most prevalent gastrointestinal symptom (26%) and the most common comorbidities were diabetes mellitus (30%) and hypertension (38%). According to the charlson comorbidity index, 30% of the patients had mild risk, 46% had moderate risk, 20% had high risk

and 4% had very high risk. In terms of COVID-19 disease severity, 47% of our patients had mild, 38% moderate and 15% severe disease. Demographic findings, symptoms, comorbidities, Charlson comorbidity index and disease severity were not statistically significant in terms of hepatotoxicity. Among the symptoms, loss of appetite (p=0.027) and abdominal pain (p=0.010) and disease severity (p=0.000) were statistically significant for mortality. While the average total hospital stay was 11.8 ± 4.6 days (min.6-max.24), extended hospitalization time was found to be significant for mortality (p=0.029). Details of demographic data and clinical findings are presented in table 1.

Table 1. Effects of Demographic Data and Clinical Findings on Liver Toxicity and Mortality

Characteristics		Hepatotoxicity (-)	Hepatotoxicity (+)	p	Survived	Death	p
Age	<65 years	37	25	0.254	59	3	0.135
	≥65 years	26	12		33	5	
Sex	Male	28	21	0.163	45	4	0.620
	Female	35	16		47	4	
COVID-19 Disease Severity	Mild	31	16	0.846	47	0	**0.000**
	Moderate	23	15		38	0	
	Severe	9	6		7	8	
Lack of appetite		16	10	0.519	21	5	**0.027**
Nausea		5	2	0.484	6	1	0.453
Vomiting		1	1	0.605	2	0	0.846
Abdominal pain		5	2	0.484	4	3	**0.010**
Diarrhea		5	1	0.275	6	0	0.598
Charlson Comorbidity Index	Low	15	15	0.261	28	2	0.160
	Middle	33	13		44	2	
	High	13	7		16	4	
	Very high	2	2		4	0	
Hypertension		28	10	0.063	34	4	0.356
Diabetes Mellitus		22	8	0.119	27	3	0.450
Cardiovascular Diseases		11	6	0.552	15	2	0.409
Chronic Lung Diseases		12	3	0.115	15	0	0.259
Neurological Diseases		5	2	0.484	5	2	0.096
Cancer		12	6	0.472	16	2	0.441
Chronic Kidney Diseases		3	0	0.246	3	0	0.777
Chronic Liver Diseases		1	1	0.605	2	0	0.846
Day of hospitalization		11.3 ± 4.5	12.8 ± 4.7	0.700	11.6 ± 4.6	14.8 ± 3.6	**0.029**

Favipiravir was used as an antiviral drug in all our patients, and in 47% of the patients, favipiravir was used for longer than the 5th day. Low molecular weight heparin (LMWH) was used for anticoagulant treatment in 96% of our patients, and methyl-prednisolone was used for anti-inflammatory treatment in 38% of our patients. The most commonly used antibacterial agent is ceftriaxone with 19%. It was discovered that favipiravir use for longer than five days was associated with a substantial increase in mortality and hepatotoxicity (p = 0.044 and p = 0.020, respectively). Only the use of antibiotics belonging to the carbapenem group was revealed to be significant for death (p = 0.001) when compared to other medical therapies. According to laboratory

results, hepatotoxicity was shown to be significantly indicated by high LDH values on days 3, 5, and 7 (p = 0.008, p = 0.002, p = 0.015, respectively) and high ALP levels on days 5 and 7 (p = 0.002, p = 0.001, respectively). High ALP values (p=0.040, p=0.002, respectively) recorded on days 1 and 7 were found to be relevant with death. Furthermore, in 6 (75%) of the 8 individuals whose illness process resulted in death, hepatotoxicity was discovered; this finding was shown to be statistically significant (p = 0.028). Details of medical treatment and laboratory findings are presented in table 2.

Table 2. Effects of Medical Treatment and Laboratory Findings on Liver Toxicity and Mortality

Characteristics		Hepatotoxicity (-)	Hepatotoxicity (+)	p	Survived	Death	p
Favipiravir	≤5 day	38	15	**0.044**	52	1	**0.020**
	>5 day	25	22		40	7	
Low Molecular Weight Heparin		61	35	0.473	89	7	0.287
Methyl prednisolone		21	17	0.149	33	5	0.135
Ceftriaxone		9	10	0.097	17	2	0.472
Piperacillin-tazobactam		11	7	0.528	16	2	0.441
Carbapenems		9	4	0.433	8	5	**0.001**
Anakinra		12	11	0.164	19	4	0.079
Elevated Alanine Amino-transferases	1 day	2	17	**<0.001**	16	3	0.174
	3 day	1	22	**<0.001**	20	3	0.267
	5 day	2	25	**<0.001**	24	3	0.370
	7 day	9	29	**<0.001**	35	3	0.644
Elevated Aspartate Amino-transferases	1 day	4	16	**<0.001**	17	3	0.196
	3 day	5	17	**<0.001**	20	2	0.564
	5 day	3	19	**<0.001**	21	1	0.438
	7 day	8	22	**<0.001**	27	3	0.450
Elevated Lactate Dehydrogenase	1 day	23	14	0.075	4	4	0.150
	3 day	20	17	**0.008**	3	5	0.450
	5 day	14	23	**0.002**	6	2	0.056
	7 day	21	16	**0.015**	3	5	0.423
Elevated Alkaline Phosphatase	1 day	10	27	0.097	4	4	**0.040**
	3 day	11	26	0.084	4	4	0.058
	5 day	16	21	**0.002**	4	4	0.105
	7 day	16	21	**0.001**	2	6	**0.002**
Elevated Gamma Glutamyl Transferase	1 day	1	15	**<0.001**	12	4	**0.021**
	3 day	1	15	**<0.001**	14	2	0.376
	5 day	2	17	**<0.001**	16	3	0.174
	7 day	2	17	**<0.001**	16	3	0.174

DISCUSSION

During SARS-CoV-2 infection, abnormal liver blood tests can happen to nearly half of the patients. It was shown that both AST and ALT were frequently high during COVID-19 (58.4% and 39.0% of patients, respectively) in a large research with 5700 patients (5). Another study by Cai Q et al. found that 41% of patients had an abnormality in liver function tests.

It was found that GGT can increase up to 3-fold, especially in severe SARS-CoV-2 infections, but this was not accompanied by an increase in ALP (6). According to a systematic analysis, 25% of the 2541 COVID-19 patients had high AST and/or ALT, 20% had elevated LDH, 3% had elevated bilirubin, and nearly all of the patients had normal ALP (7). In our study, we found the rate of liver damage to be 37%.

Increased liver enzymes were found in 15,407 COVID-19 patients in a meta-analysis; these patients had increased liver enzymes 23.1% at the beginning of the disease and 24.4% over the course of the illness (8). The proportion of patients with increases in both ALT and AST ranged from 12.6% in mild instances to 46.2% in severe cases, according to another study detailing temporal changes along the course of COVID-19 disease. Most patients had an ALT increase between days 4 and 17 of hospital stay; in severe cases, this occurred on average after 7.3 days, whereas in moderate ones, it occurred on average after 10.7 days. The majority of patients had relatively modest, isolated increases in their ALT and AST levels during treatment, and the majority of them were released with normal liver marker values (9). In our study, in addition to the elevations of AST-ALT and GGT, the elevations of LDH on days 3, 5 and 7, and ALP on days 5 and 7 were found to be significant for liver damage.

Cai Q et al. it has been shown that more than 10% of COVID-19 patients have increased liver enzyme levels during hospitalization and this can be attributed to the medications used (6). Kulkarni et al. conducted a meta-analysis comprising 20,874 COVID-19 participants, revealing that the incidence of drug-induced liver injury was 25.4% (8). Of the 53 patients in a case study looking at the use of remdesivir to treat COVID-19, 23% experienced increases in liver enzymes that led to an early stop to therapy (10). Unlike our study, it was conducted with favipiravir and was found to be significant for both hepatotoxicity and mortality when used for more than 5 days.

More severe COVID-19 infections were linked to higher ALT, AST, and bilirubin levels, according to a meta-analysis that examined 3428 patients in total (11). A nine-fold increased risk of severe infection was estimated to be linked to liver damage after COVID-19 infection in another large-scale investigation (6). Increases in these parameters have been linked in other studies to worse lung CT scores, a higher number of patients needing ICU care, longer hospital stays, and mortality (12, 13). The prevalence of elevated liver markers in COVID-19-related deaths ranges from 58% to 78% (4). Our study found the liver damage rate of patients who died as a result of the COVID-19 process to be 75% and found that prolonged hospitalizations and liver damage had an impact on mortality.

Limitations of the study

The fact that the study was based on retrospective data was possibly its biggest drawback. Further limitations to our study include the non-uniform distribution of patients' ages, concurrent medical conditions, and medication use, as well as the absence of imaging methods like computed tomography and ultrasonography to rule out structural pathologies of the liver, pancreas, and biliary tract.

CONCLUSIONS

Our study concluded that liver damage due to any cause may occur in a significant portion of COVID-19 patients, especially those treated in hospital, and that these patients carry a serious risk of mortality. In such a situation, it is important to first rule out or confirm drug-induced liver injury and provide comprehensive evaluations, including regular liver tests, especially when treating and monitoring patients with risk factors. On the other hand, it is clear that more comprehensive, multi-center, prospective-observational studies with large participation are needed to fully understand this issue and especially to determine its relationship with drugs used in the treatment of COVID-19.

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Conflict of Interest

Authors declare no conflicts of interest

Support Resources

No financial support was used by authors during this study.

Ethical Declaration

Ethical permission was obtained from the Cukurova University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date March 4, 2022 and number 48/120, and Helsinki Declaration rules were followed to conduct this study.

Authors contributions

Concept: EG, Design: EG, Supervising: EG, Financing and equipment: EG, Data collection and entry: EG, Analysis and interpretation: EG, Literature search: EG, Writing:
EG, Critical review: OBT,KA.

A part of this study was presented as an oral presentation titled "COVID-19 RELATED LIVER INJURY: A SINGLE CENTER EXPERIENCE" at the "CUKUROVA 10th INTERNATIONAL SCIENTIFIC RESEARCH CONFERENCE" held in Adana, Adana, Turkey.

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Scientific Reports in Medicine

RESEARCH ARTICLE

Central Line Associated Bloodstream Infections Outside the Intensive Care Unit: A 2-Year Analysis

Catheter Associated Bloodstream Infections Outside Intensive Care Unit

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Abstract:

Objective: There is limited data on the rates of central line associated bloodstream infections (CLABSI) and the characteristics of these infections in units other than intensive care units (ICU). Our aim in this study was to determine the rates and features of CLABSI in non-ICU units.

Method: In our hospital, CLABSI surveillance is performed according to CDC criteria in Internal Medicine Nephrology, Hematology, Oncology, Pediatric Hematology, Oncology and hematopoietic stem cell transplant (HSCT) units other than ICUs. Hospital infections control committee surveillance data is used in this study.

Results: In a total of 70028 patient days and 22358 catheter days, 101 infections were detected in 94 patients. The CLABSI rate was 1.44/1000 patient days, the incidence density was 4.2/1000 catheter days, and the device utilization rate was 0.32. The highest infection rate was observed in the adult HSCT unit (15.18/1000 patient days). 56.4% of the patients were male (n=53) and the mean age of the patients was 32±2.5 years. The mean length of hospitalization was 27.7±2.5 days. Half of the patients (n=47) had permanent and half had transient central lines. When the underlying factors were analyzed, hematologic cancer was found in 54.7% and hemodialysis in 19.2%. Of the 94 infection episodes, 21.8% were polymicrobial. Of the 125 microorganisms isolated, 61.6% were Gram negative, 20.8% were fungi and 17.6% were Gram positive. The most frequently isolated pathogens were *Escherichia coli* (n=17, 13.6%) and *Klebsiella pneumoniae* (n=17, 13.6%), followed by *Staphylococcus aureus* (n=10, 8%) and Candida parapsilosis (n=9, 7.2%). Crude mortality was 36.2% (n=34). Colistin and amikacin were the most effective antibiotics in *E.coli* and *K.pneumoniae*, oxacillin resistance was found as 60% (6/10) in *S. aureus* isolates. In *Candida* species, fluconazole resistance was 15.8% (3/19).

Conclusion: It is important to recognize that CLABSIs can also occur in non-ICU patients, and particularly in the population with hematological cancers, monitoring the rates and identifying risk factors specific to this population are crucial for implementing infection control measures.

Keywords: Central venous catheter, Central line, Infection rate, Non-intensive care unit

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INTRODUCTION

Bloodstream infections are among the most common infections in hospitals (1). Central venous catheter associated bloodstream infection rates vary according to the size of the hospital, the clinic where the patient is hospitalized and the type of catheter (2). Since central venous catheters are the most common cause of infection, central line associated bloodstream infections (CLABSIs) are the most common infections in hospitals today and are particularly important for patients hospitalized in intensive care units (ICUs) due to their high morbidity, mortality, and increased costs (3). Most of the studies on the detection and prevention of CLABSIs have been conducted in ICUs. According to the data of a consortium of developing countries, the rates of CLABSI vary between 1.44 and 20.90/1000 catheter days depending on the type of ICU (4). In Turkey, the Ministry of Health established the national nosocomial infection surveillance system in 2007 and has been collecting data electronically from hospitals across the country since 2008 (5). However, reports from non-ICU settings are very limited and there are no specific recommendations for the prevention of HAIs in these areas (6). The aim of this study was to determine the rates of CLABSI outside the ICUs in our hospital and to identify specific risk factors to shed light on future infection control measures.

METHOD

Patients

In addition to the ICUs in our hospital, CLABSI surveillance is performed in Nephrology, Hematology/Oncology, Pediatric Hematology/Oncology and Hematopoietic Stem Cell Transplantation units. Patients from these units where surveillance was performed in 2015-2016 were included in the study and data were extracted retrospectively from Hospital Infection Control Committee's (HICC) patient follow-up forms. Hospital infections control committee surveillance data is used in this study.

Surveillance

Surveillance in the relevant units is prospective and laboratory-based, and data are recorded on patient tracking forms. The data used include dates of hospitalization, dates of diagnosis and development of infection, underlying diseases, interventional procedures and risk factors, microorganisms grown and susceptibility characteristics. Nosocomial infection diagnoses are made by infection control nurses and physicians according to the Center for Disease Control (CDC) nosocomial infection diagnostic criteria (7).

The number of inpatients, patient days and catheter days were recorded in the surveillance units. CLABSI rate was calculated by dividing the number of infections by patient days and multiplying by 1000, and infection incidence density was calculated by dividing the number of infections by catheter days and multiplying by 1000. Catheter utilization rate was calculated by dividing catheter days by patient days.

Microbiology

Samples obtained from patients for blood culture were inoculated into BACTEC Plus Aerobic/F blood culture bottles (Becton Dickinson Diagnostic Instrument Systems, Sparks, USA) and incubated in the BACTEC FX system (Becton Dickinson, USA) for seven (7) days. Blood culture bottles that showed a positive signal due to growth were passaged onto 5% sheep blood agar, chocolate agar and Eosin Methylene Blue (EMB) agar media. These media were obtained from Biomerieux company. The plates were incubated at 37°C, aerobic and 5% CO2 for 24-48 hours and the microorganisms grown were preliminarily identified by classical microbiological methods such as colony morphology, Gram staining, catalase test, oxidase test and coagulase test. Further identification was performed using Gram Positive (GP), Gram Negative (GN) and Yeast (YST) identification cards in the automated Vitek-2 System (Biomerieux, France). All microorganisms from all episodes are included to the study.

Statistics

The data were transferred to the computer environment with SPSS v20.0 program and descriptive analysis was performed. Data were presented as mean (mean) ± standard deviation (SD), median, lower value (LV), upper value (UV), number (n) and percentage (%).

RESULTS

In a total of 94 patients, 101 CLABSIs were detected in 70,028 patient days and 22,358 catheter days. CLABSI rate was calculated as 1.44/1000 patient days, CLABSI incidence density as 4.2/1000 catheter days, and central venous catheter utilization rate as 0.32 (Table 1). CLABSI rates and incidence densities according to departments are shown in Table 2. The highest infection rate was observed in the adult bone marrow transplantation unit.

Table 1. Central line associated bloodstream infection (CLABSI) rates by years

	Number of patients	Patient day (PD)	Catheter day (CD)	Number of CLABSI	CLABSI * rate / 1000 PD†	CLABSI Incidence density / 1000 CD‡	CVC§ utilization rate
2015	44	34174	11350	49	1.4	3.88	0.33
2016	50	35854	11008	52	1.45	4.54	0.31
Total	94	70028	22358	101	1.44	4.2	0.32

* Central venous catheter-associated bloodstream infection
† patient day
‡ catheter day
§ central venous catheter

Table 2. Rate and incidence densities of central venous catheter-associated bloodstream infections according to departments.

	Patient day	Catheter day	Number of infections	Infection Rate	Incidence density	Utilization rate
Oncology	13038	3143	18	1.38	5.73	0.24
Hematology	12022	2010	12	1	5.97	0.17
Pediatric Oncology	13319	5189	14	1.05	2.7	0.39
Pediatric Hematology	13069	4861	19	1.45	3.91	0.37
Nephrology	13878	4019	15	1.08	3.73	0.29
Adult HSCT*	2019	922	14	6.93	15.18	0.46
Pediatric HSCT*	2683	2214	9	3.35	4.06	0.82
Total	70028	22358	101	1.44	4.2	0.32

* Hematopoietic stem cell transplant

56.4% of the patients were male (n=53), the mean age was 32±2.5 years, and the median age was 31 (0-90).

The mean length of hospitalization was 27.7±2.5 and the median length of stay was 20 (4-148) days. Half of the patients (n=47) had permanent and half had transient catheter-related bloodstream infections. When the risk factors of the patients were analyzed, hematologic cancer was found in 54.7%, hemodialysis in 19.2% and other possible risk factors are summarized in Table 3.

Table 3. Risk factors of 94 patients with central venous catheter-associated bloodstream infections

Risk factors	N	%
Transfusion	75	79.8
Hematologic malignancy	54	57.4
Indwelling catheter (port or Hickman)	50	53.2
Temporary central venous catheter	48	51.1
Urinary catheter	36	38.3
H2 receptor blocker	35	37.2
Neutropenia	29	30.9
Malignant solid tumor	20	21.3
Hemodialysis	18	19.2
Total parenteral nutrition	17	18.1
Hypertension	6	6.4
Chronic kidney disease	6	6.4
Infection on admission	4	4.3
Autoimmune diseases	4	4.3
Peripheral arterial catheter	3	3.2
Diabetes mellitus	1	1.1

Of the 94 infection episodes, 21.8% were polymicrobial. Of the 125 microorganisms isolated, 62.4% were Gram negative, 20% were fungi and 17.6% were Gram positive. The most frequently isolated pathogens were *Escherichia coli* (n=17, 13.6%) and *Klebsiella pneumoniae* (n=17, 13.6%). These were followed by *Staphylococcus aureus* (N=10, 8%) and *Candida parapsilosis* (N=9, 7.2%) (table 4). Crude mortality was 36.2% (n=34).

While colistin and amikacin were the most effective antibiotics in *E.coli* and *K.pneumoniae*, amikacin and ciprofloxacin were found in P.aeruginosa. High resistance rates were observed in *A.baumannii.* Resistance rates were low in *S.maltophilia* (Table 5). In Gram positive microorganisms, *Staphylococcus aureus* was the most common agent and oxacillin resistance was found to be 60% (6/10). Resistance to fusidic acid and ciprofloxacin was not detected (0/6 and 0/8, respectively) and 10% (1/10) to clindamycin. Fluconazole resistance in *Candida* species was 15.8% (3/19), one of the resistant fungi was *C.krusei* and 2 were *C.parapsilosis.*

DISCUSSION

"The Institute for Health Care Improvement" conducts the "Save 5 million lives" campaign by optimizing infection control, but this campaign only targets patients hospitalized in the ICU (8). Is it really possible to reduce CLABSI rates by targeting only ICU patients? In a survey study investigating the rate at which patients use central venous catheters, it was found that 55% of patients hospitalized in intensive care used central venous catheters (CVCs), while this rate was 24% in other clinics. However, considering that the majority of patients were hospitalized outside intensive care units (70%), it is understood that the majority of CVCs in this study were used in non-ICU clinics (9). In addition, there are also data indicating that catheters stayed longer in units other than intensive care units. In one study, the median catheter length of stay was reported to be 6 days in internal units, 8 days in surgical units and 3 days in ICU (10). An article published in 2004 also recommended that surveillance should be carried beyond intensive care units (11).

Table 4. Distribution of causative microorganisms.

		N	within group %	Total %
Gram positive	*Staphylococcus aureus*	10	45.5	8.0
	CNS	8	10.3	6.4
	Staphylococcus epidermidis	6	27.3	4.8
	Staphylococcus hominis	1	4.5	0.8
	Staphylococcus haemolyticus	1	4.5	0.8
	Enteroccus faecium	2	9.1	1.6
	Enterococus avium	1	4.5	0.8
	Streptococus spp.	1	4.5	0.8
	Subtotal	22	100.0	17.6
Gram Negative	*Escherichia coli*	17	21.8	13.6
	Klebsiella pneumoniae	17	21.8	13.6
	Acinetobacter baumannii	8	10.3	6.4
	Pseudomonas aeruginosa	8	10.3	6.4
	Stenotrophomonas malthophilia	8	10.3	6.4
	Enterobacter cloacea	4	5.1	3.2
	Acinetobacter lwoffi	3	3.8	2.4
	Acinetobacter junii	2	2.6	1.6
	Serratia marcescens	2	2.6	1.6
	Aeromonas sobria	2	2.6	1.6
	Acinetobacter ursingi	1	1.3	0.8
	Citrobacter koseri	1	1.3	0.8
	Enterobacter aerogenes	1	1.3	0.8
	Klebsiella oxytoca	1	1.3	0.8
	Pseudomonas stutzeri	1	1.3	0.8
	Rhizobium radiobacter	1	1.3	0.8
	Delftia acidovorans	1	1.3	0.8
	Subtotal	78	100.0	62.4
Fungus	*Candida parapslosis*	9	36.0	7.2
	Candida albicans	6	24.0	4.8
	Candida famata	4	16.0	3.2
	Candida krusei	4	16.0	3.2
	Candida tropicalis	1	4.0	0.8
	Candida guilliermondii	1	4.0	0.8
	Subtotal	25	100,0	20
Total		125		100

The first non-ICU surveillance data was published by the German nosocomial surveillance system in 2006 (12). In this study, data from 42 university and state hospitals were generated using CDC nosocomial infection diagnostic criteria. After at least 3 months of surveillance, the rate of non-ICU vehicle use was found to be 4.6%, which is considerably lower than the rate of vehicle use determined in our study (32%) and the rate found in the survey study by Climo and colleagues (24.4%) (8). The high rate in our study was attributed to the high-risk group of patients with cancer and receiving long-term chemotherapy.

Table 5. Resistance characteristics of the main Gram negative agents (n/%).

	E.coli		*K.pneumoniae* (n=15)		*P.aeruginosa* (n=8)		*A.baumannii* (n=8)		*S.maltophilia* (n=8)	
	(n=17)	%	n	%	n	%	n	%	n	%
Amikacin	3/15	20	6/15	40	0/7	0	3/8	37.5		
Ciprofloxacin	8/15	53.3	8/16	50	0/7	0	7/8	87.5		
Levofloxacin	1/1	100	0/1	0					1/5	20
Cefepime	9/15	60	13/16	81.3	2/7	28.6	4/4	100		
Ceftazidime	9/13	69.2	10/13	76.9	2/8	25			0/1	0
Meropenem	5/14	35.7	7/16	43.8	2/7	28.6	7/8	87.5		
TMP-SMZ*	8/15	53.3	13/16	81.3					1/8	12.5
Tigecyclin	0/10	0	4/7	57.1			4/8	50	0/1	0
Colistin	0/13	0	2/15	13.2	0/7	0	0/8	0	0/1	0
ESBL†	11/17	64.7	10/17	58.8						

* Trimethoprim sulfamethoxazole

† Extended spectrum beta lactamase

If we look at the incidence densities of CLABSI, Vonberg et al. found an infection rate of 4.3 infections/1000 catheter days in various internal and surgical clinics, while Marschall et al. found 5.7 infections/1000 catheter days in four general internal medicine clinics. These rates are similar to the 4.2 infections/1000 catheter days found in our study. In another recent study examining patient-related risk factors contributing to CLABSI, the infection rate was 0.35 infections / 1000 patient days, which is lower than the rate of 1.44 infections / 1000 patient days in our study. This was attributed to the fact that underlying diseases such as hematologic malignancy and neutropenia, which were also identified as risk factors in this study, were more common in our patient group.

If we look at the CLABSI rates in intensive care units throughout Turkey, we see that they vary between 0.0/1000 and 9.1/1000 catheter days in various intensive care units according to the 2019 National Healthcare Associated Infections Surveillance Network summary report. This shows that the CLABSI rates we detected in our study are comparable to intensive care rates and supports the idea of moving surveillance beyond intensive care units (13).

In a 10-year study from Spain investigating CLABSI mortality risk factors in non-ICU patients, the infection rate was found to be 0.23/1000 patient days and the causative agents were Gram-positive cocci (70.1% cases), Gram-negative bacilli (31.1%) and Candida species (1%) (14). In our study, a very low infection rate and different agents are noteworthy. The low infection rate was attributed to the fact that almost half of the catheters in the study were peripheral catheters with low infection risk and the risky patient population in our study. Looking at the details of our study, the highest infection rate was observed in the adult bone marrow transplantation unit. Again, the reason why gram-negative bacteria and fungi were more common as causative agents was thought to be the high number of immunosuppressed patients in our study. In another study, 23 non-ICU CLABSIs occurred. The incidence rate was 1.2 per 10,000 bed days. When we interpret this rate, which is considerably lower than our study, we attribute it to the fact that the number of immunosuppressed patients in this study was only half of the total patients. In this study, a total of 26 microorganisms were isolated and similar to our study, Gram-negative bacilli were found to be more common than Gram-positive cocci (15).

A recent, 3-year case-control study examining the incidence and risk factors for CLABSI in hematologic and oncologic patients included a total of 610 patients, with 10.6 cases per 1,000 CVC days. Multiple CVC use per case, CVC implantation for stem cell transplantation, acute myeloid leukemia, leukocytopenia (≤ 1000/μL), carbapenem therapy and pulmonary diseases were found to be independent risk factors (16). This rate is much higher than our study and the causative agents were Gram-positive with 94.6%, again very different from our study. In another study examining the causative agents in oncologic and hematologic patients, it was shown that the epidemiology of CLABSI has changed: The proportion of Gram-negative bacteria increased over time (from 11.9% to 29.4%; p<0.001), and the absolute number and proportion of multidrug-resistant Gram-negative bacteria also increased (from 9.5% to 40.0%; p=0.039). *Pseudomonas aeruginosa* increased and constituted up to 40% of all Gram-negative bacteria (17). In our study, the most common microorganism was *Acinetobacter baumannii*, which attracted attention with its high resistance rate. This difference was attributed to the fact that it constituted the flora of our hospital as the most common agent in almost all units.

In a study examining the changing epidemiology in cancer patients, a previous cohort (cohort 1) of similar cancer patients who had BSI at the same institution between September 1999 and November 2000 was compared with the current cohort (cohort 2). When the 2 cohorts were compared, it was observed that the frequency of gram-negative organisms as the etiologic agent of CLABSI increased significantly from 24% in cohort 1 to 52% in cohort 2 (P < 0.0001) (18).

According to a study from Israel, there has also been a linear shift towards the predominance of Gram-negative bacilli (p<0.001 for trend). In 1996, 68% (68/100) of CLABSIs were caused by Gram-positive cocci, while in 2012, 77.8% (28/26) were caused by Gram-negative bacilli. The shift towards Gram-negative CLABSIs and the associated mortality necessitates that empirical treatment for CRBSIs should be guided by local epidemiology (19).

Limitations of the study

The limitations of our study are that it included data from a single center and mortality and risk factor analysis could not be performed due to lack of data.

CONCLUSION

In conclusion, we observe that catheter-associated bloodstream infection rates are comparable to those in intensive care units, especially in non-ICU clinics where immunosuppressed patients are followed. Although the idea that CLABSI rates in non-ICU clinics should be monitored is not new, there is no sufficient data on this subject to date. It is important to monitor CLABSI rates in units with high catheter utilization rates even if they are not intensive care units. Due to inter-institutional patient population and practice differences, CLABSI mortality and infection risk factors should be studied in each institution and necessary infection control measures should be taken.

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Conflict of Interest

Authors declare no conflicts of interest.

Support Resources

No financial support was used by authors during this study.

Ethical Declaration

Ethical permission was obtained from the Medical Faculty Clinical / Human Research Ethics Committee for this study with date 17/04/2017 and number 63/3 and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AC, YT Design: AC, Supervising: BK, FK, YT, Data collection and entry: AC, DE, FK, Analysis and interpretation: MK, HD, FK, BK Literature search: AC, ASI, BK, Writing: AC, Critical review: AC, BK, FK, SK, FK, DE, ASİ, YT.

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RESEARCH ARTICLES

Evaluation of Occupational Health Literacy of Health Workers in Adana, Turkey*

Occupational Health And Safety Literacy In Healthcare Workers

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Abstract:

Objective: The importance of occupational health and safety (OHS) and related health literacy is increasing. The aim of this study was to evaluate the occupational health literacy status of healthcare workers in Adana (Turkey).

Method: The population of the study consists of health workers in Adana province (N=18,660). Between April 29 and June 13, four researchers visited the workplaces of health workers and asked them to answer online survey questions through the WhatsApp application in face-to-face meetings. The study was completed with 179 individuals determined using non-probability sampling method. The analyses were performed using the SPSS 22 software. The Kolmogorov-Smirnov, t test in independent groups Mann-Whitney U test, ANOVA, and Kruskal-Wallis test were used in the analyses. A significance level of $p < 0.05$ was considered statistically significant.

Results: The study included 179 healthcare workers with an average age of 32.36±7.97 years. Pre-employment medical examinations and periodic examinations were reported to have been performed in 65.9% and 50.3%, respectively. The "Occupational Health Literacy Scale" that was administered to the participants with a resulting avarage score was 80.30±11.68. Participants who underwent workplace periodic examinations had higher scores in Factor 1 and Factor 4 compared to those who did not undergo any periodic examination.

Conclusion: Participants who underwent periodic examinations and those who were informed about health risks had higher occupational health literacy. It is recommended that health workers be informed about health risks in the institutions they work, periodic examinations are carried out regularly, OHS trainings are planned, and these trainings are repeated periodically.

Keywords: Occupational Health, Occupational Safety, Healthcare Worker

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INTRODUCTION

According to the World Health Organization (WHO), health is defined as not merely the absence of disease or disability but a state of complete physical, mental, and social well-being (1). Occupational Health and Safety (OHS) involves systematic and scientific efforts to protect against conditions in the workplace that could be harmful to health due to various reasons and to improve existing health and safety conditions (2). In our country, activities related to ensuring health and safety in the workplace gained momentum with the enactment of Law No. 6331 on Occupational Health and Safety in 2012. The purpose of this law is to regulate the duties, authorities, responsibilities, rights, and obligations of employers and employees to ensure occupational health and safety and to improve the existing health and safety conditions in workplaces (3).

Healthcare workers, including doctors, nurses, midwives, laboratory technicians, health technicians, public health workers, and traditional medicine practitioners, are individuals engaged in occupational activities primarily aimed at improving health (4). The term also encompasses healthcare management and support workers, such as cleaners, drivers, hospital administrators, regional health managers, and social workers, as well as other professional groups involved in health-related activities as defined by the International Standard Classification of Occupations. Healthcare workers face a range of occupational risks related to infections, unsafe patient handling, hazardous chemicals, radiation, heat, noise, psychosocial hazards, violence, harassment, injuries, and inadequate provision of safe water, sanitation, and hygiene (4). Due to the increased level of risk associated with all these factors in healthcare service delivery, hospitals are classified as highly hazardous under Law No. 6331

OHS (5). Ensuring a healthy and safe working environment in healthcare services is crucial for preventing occupational accidents and diseases, positively impacting the health and safety of employees, and enhancing their work efficiency and well-being from their social life to the service they provide (6).

Occupational health literacy refers to the degree to which individuals have the capacity to obtain, process, and understand essential Occupational Health and Safety (OHS) information and services in order to make appropriate decisions regarding health and safety in the workplace (7).The development of occupational health literacy is crucial for preserving the health of employees and preventing negative outcomes such as workplace accidents, near-miss incidents, occupational diseases, and work-related illnesses that may arise from workplace conditions. Studies have shown that employees with weak occupational health literacy have higher rates of work-related injuries, illnesses, and fatalities (8). There is no study evaluating occupational health literacy among healthcare workers in our country.

This study aims to assess the occupational health literacy of healthcare workers in Adana.

METHOD

This study is a cross-sectional research conducted in May 2023 in Adana. The study population consists of healthcare workers in Adana province (N=18,660). The required sample size was calculated using G power 3.1 program with P=0.5, effect size=0.1, power=80%, and CI=95%, resulting in a sample size of 199. As it was not possible to access a list of registered healthcare workers in Adana, a non-randomized sampling method (non-probability sampling - convenience sampling) was chosen. Interviews were conducted with 200 healthcare workers to administer the survey, but 21 individuals refused to participate for various reasons. Therefore, we were able to reach 90% of the selected sample (179 individuals) through convenience sampling. From April 29th to June 13th, the study was conducted

with four researchers visiting healthcare workers at their workplaces and explaining the purpose face-to-face. Due to the workload of healthcare workers, an online survey was prepared using Google Forms and sent through WhatsApp to collect their responses. Due to the short duration of the project, we couldn't reach the entire sample size.

The first part of the questionnaire includes sociodemographic questions such as age, gender, marital status, education level, and profession-related information. It also includes questions related to the workplace, such as the institution where the respondent works, the work area, years of experience, the use of personal protective equipment in the workplace, history of workplace accidents, occupational diseases, near-miss incidents, work-related infections, and any work-related health issues experienced.

Furthermore, it contains questions about the participants' engagement with occupational health and safety aspects, including whether they have received training on occupational health and safety, if they hold any position related to occupational health and safety, if they have been informed about health risks related to their work area, and whether they undergo pre-employment and periodic health examinations.The second part of the questionnaire is the Occupational Health Literacy Scale (OHLS) (9). OHLS was developed by Suthakorn et al. and its Turkish validity and reliability study were conducted by Uskun et al. in 2022 (9). The internal consistency coefficient, Cronbach's Alpha, was calculated to determine the reliability of the scale and found to be 0.93.

OHLS is a Likert-type scale consisting of 38 items, divided into 4 subscales, designed to measure employees' ability to access, understand, evaluate, use, and communicate information related to OHS based on their self-reported responses.

The four subscales are as follows: Factor 1 evaluates the ability to access OHS information and consists of questions 1 to 7; factor 2 assesses the ability to understand OHS information and includes questions 8 to 22; factor 3 encompasses the evaluation of OHS information and consists of questions 23 to 27; factor 4 evaluates the use and communication of OHS information and includes questions 28 to 38.

Participants are required to rate their responses on a scale from 1 (least appropriate) to 3 (most appropriate). The total score is then used for evaluation. The lowest possible score on the scale is 38, while the highest is 114. A higher score indicates a higher level of occupational health literacy (9).

Statistical analysis: The data analysis was performed using SPSS 22 program. For qualitative data, the results are presented in numbers and percentages, while for quantitative data, they are reported as arithmetic mean, standard deviation, and median. The normal distribution test used was the Kolmogorov-Smirnov Test.

Various statistical tests were used in the analyses, including t-test in independent groups, Mann-Whitney U test, ANOVA (Analysis of Variance), and Kruskal-Wallis test. For post-hoc tests, the Bonferroni and Tamhane tests were utilized. The significance level chosen for statistical analysis was $p < 0.05$, which means that results with p-values less than 0.05 were considered statistically significant.

Ethics Approval: Approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Cukurova University Faculty of Medicine, with protocol number 133, on May 5, 2023.

RESULTS

The mean age of the 179 healthcare workers included in our study is 32.36 ± 7.97 years. Among the participants, 67% are female, and 65.4% have a work experience of 10 years or less. Table 1 presents the sociodemographic characteristics and some other information of the individuals.

Table 1. Sociodemographic characteristics	
Characteristics	**n (%)**
Gender	
Female	120(67)
Male	59(33)
Age	32,36±7,97
Marital Status	
Married	109(60,9)
Single	65(36,3)
Other	5(2,8)
Education Level	
High school	11(6,1)
Assosiate's degree	5(2,8)
Bachelor's degree	61(34,1)
Masters-Ph.D	102(57)
Occupation	
Doctor	106(59,2)
Nurse	48(26,8)
Other	25(14)
Institution of employment	
PHC	12(6,7)
GH	48(26,8)
UH	101(56,4)
HD	18(10,1)
Years of employment	
≤10 years	117(65,4)
11-20 years	37(20,7)
≥21 years	25(13,9)
Total	179(100)

PHC: Primary Health Care Center GH: Goverment Hospital UH: University Hospital HD: Health Directorates

According to Table 2, among the healthcare workers who participated in our study, 16.2% experienced a workplace accident, 13% experienced a near-miss incident, 23.5% had a work-related infectious disease, and 8.9% had a work-related health problem. None of the participants were diagnosed with an occupational disease (Table 2). Among those who experienced a workplace accident and near-miss incident, the most common type of accident was needlestick injuries (n: 22, 73.3%) and the most common near-miss incident was also needlestick injuries (n: 7, 50%). Among the participants who reported work-related health problems, the most frequently mentioned issue was related to the musculoskeletal system. Among those who had a work-related infectious disease, the most commonly reported infection was Covid-19.

Table 2. Occupational Health and Safety Issues Experienced by Participants Characteristics	
Characteristics	**n (%)**
History of work accidents	
Yes	29(16,2)
No	150(83,8)
Diagnosis of occupational disease	
Yes	0(0)
No	179(100)
Occurrence of near miss	
Yes	13(7,3)
No	126(70,4)
Unknown	40(22,3)
History of work-related infections	
Yes	42(23,5)
No	137(76,5)
Experience of work-related health problems	
Yes	16(8,9)
No	163(91,1)
Total	179(100)

According to Table 3, 68.7% of the healthcare workers who participated in our study have received occupational health and safety training at their workplace. 66.5% of the participants have been informed about health risks related to their work unit. Regarding health examinations, 65.9% of the participants underwent pre-employment health examinations, and 50.3% had periodic health examinations.

Table 3.Occupational Health and Safety Practices in the Workplace Features	
Characteristics	**n (%)**
Status of receiving OHS training	
Yes	123(68,7)
No	56(31,3)
Informing about health risks	
Yes	119(66,5)
No	60(33,5)
Status of pre-employment medical examination	
Yes	118(65,9)
No	61(34,1)
Status of periodic medical examination	
Yes	90(50,3)
No	89(49,7)
Involvement in OHS activities	
Yes	10(5,6)
No	169(94,4)
Total	179(100)

The participants' scores on the OHLS ranged from a minimum of 42 to a maximum of 109. The mean score was 80.3 ± 11.68.

There were no statistically significant differences among education levels for Factor 1, Factor 2, Factor 3, and Factor 4, as well as for the total OHLS score

(p=0.230, p=0.214, p=0.674, p=0.703, p=0.907). However, there was a significant difference in Factor 4 scores between doctors and other healthcare workers, with doctors scoring lower (p=0.014).

When examining the work experience of participants, there were significant differences in Factor 2, Factor 4, and the total OHLS score among groups with different work experience durations (≤5 years, 6-20 years, and ≥21 years) (p=0.01, p=0.007, p=0.008). However, no significant differences were observed for the other factor scores (Factor 1 and Factor 3) (p=0.664, p=0.051). Post-hoc analysis revealed that the scores for Factor 2, Factor 4, and the total OHLS score were higher among participants with work experience of ≥21 years compared to those with work experience of ≤5 years and 6-20 years. This suggests that participants with longer work experience have higher occupational health literacy scores in terms of Factor 2 and Factor 4, as well as the overall OHLS score.

Among the different working institutions (PHC, GH, UH, HD), there was a significant difference in Factor 1 scores (p=0.037). The post-hoc analysis has shown that GH and HD employees have significantly higher Factor 1 scores compared to PHC employees.

This indicates that workers in the PHC institution have lower occupational health literacy scores in terms of Factor 1 compared to workers in GH and HD institutions.

When examining the occupational health issues and practices experienced by the workers, no significant differences were found in the scores for each sub-factor (Factor 1, Factor 2, Factor 3, and Factor 4), as well as the total OHLS score, between those who had experienced a work accident and those who hadn't (p=0.732, p=0.993, p=0.328, p=0.898, p=0.729). Similarly, there were no significant differences in the scores between those who had experienced a near-miss incident and those who hadn't (p=0.662, p=0.314, p=0.067, p=0.502, p=0.263), those who had experienced a work-related infection and those who hadn't (p=0.400, p=0.452, p=0.989, p=0.502, p=0.873), those who had experienced a work-related health problem and those who hadn't (p=0.423, p=0.582, p=0.992, p=0.488, p=0.486), those who were involved in occupational health and safety studies and those who weren't (p=0.899, p=0.471, p=0.441, p=0.813, p=0.753), and those who had undergone a pre-employment medical examination and those who hadn't (p=0.112, p=0.308, p=0.220, p=0.652, p=0.513).

Significant differences were found in Factor 1, Factor 4, and total OHLS scores between workers who underwent workplace periodic medical examinations and those who did not (p=0.005, p=0.004, p=0.025).

Regarding the workers who were informed about the health risks in their workplace compared to those who were not informed, significant differences were observed in Factor 1, Factor 2, Factor 4, and total OHLS scores (p=0.000, p=0.019, p=0.007, p=0.002). In terms of Factor 1 scores, a significant difference was found between different work areas (p=0.037); post-hoc analysis revealed that administrative staff had significantly higher Factor 1 scores compared to those who worked in multiple areas. The results of the analyses are presented in Table 4.

DISCUSSION

In this study conducted on healthcare workers, 68.7% of the participants stated that they received OHS training. In another study conducted on healthcare workers of a hospital in 2020, the rate of those who received OHS training was found to be 20.5% (10). The findings show a difference from our study.

The rate of participants who had an pre-employement examination was 65.9%, while the rate of participants who had a periodic examination was found to be 50.3%. In a study conducted by Özberk et al., published in 2021, it was found that 70.9% of healthcare workers had an entry examination and 42.7% had regular periodic examinations (11). The findings show similarity with our study.

Table 4. OHLS Analysis of Total Score and Scale Subfactors According to Participant Characteristics					
	Factor 1	Factor 2	Factor 3	Factor 4	OHLS Total
	X±SS /Median(IQR)[a]				
Gender					
Male	12(2)	37(10)	8(1)	23(6)	80,54±12,02
Female	13(3)	36,5(9)	8(2)	24(5)	79,81±11,06
p	0,338	0,621	0.850	0.860	0,696
Education level					
High school	14(2)	34(8)	8(0)	24(8)	78,91±7,51
Assosiate's degree	14(2)	30(7)	8(3)	23(5)	79,40±11,92
Bachelor's degree	13(3)	36(10)	8(3)	24(8)	81,13±13,96
Master's/Ph.D	13(3)	37(9)	8(1)	23(5)	80±10,62
p	0,230	0,214	0,674	0,703	0,907
Occupation Groups					
Doctor	13(3)	36(9)	8(2)	23(5)	79,06±10,5
Other healthcare workers	13(3)	37(10)	8(2)	24(7)	82,28±13,19
p	0,123	0,852	0,206	0,014	0,073
Institution of employment					
Primary Healthcare Center	11,5(4)[c]	37(12)	8(2)	23(5)	77,5(17)
Goverment Hospital	13,5(2)[c]	36(10)	8(2)	24(5)	79(15)
University Hospital	13(3)	36(10)	8(2)	23(6)	80(15)
Health Directorates	13,5(4) [c]	37,5(10)	9(4)	24,5(9)	85(19)
p	0,037	0,609	0,235	0,150	0,308
Years of employment					
5 Years and below	13(2)	35(9)	8(1)	23(4)	79(11)
6-20 Years	13(3)	37(10)	8(2)	23(6)	79(16)
21 Years and above	12(4)	40(6)[b]	8(4)	27(8)[b]	90(20)[b]
p	0,664	0,01	0,051	0,007	0,008
Work accident experience					
Yes	12(3)	36(8)	8(2)	24(7)	80,97±9,31
No	13(3)	37(10)	8(2)	23,5(5)	80,17±12,11
p	0,732	0,933	0,328	0,898	0,739
Near-miss experience					
Yes	13(4)	39(4)	9(4)	25(7)	85,31±10,46
No	13(3)	36(10)	8(3)	23(5)	80,08±15
Unknown	13(3)	36(8)	8(1)	23,5(6)	79,38±11,29
p	0,662	0,314	0,067	0,502	0,502
Work-related infectious disease experience					
Yes	12(4)	37(10)	8(2)	23(4)	80,05±11,83
No	13(3)	36(10)	8(2)	24(6)	80,38±11,68
p	0,400	0,452	0,989	0,502	0,873
Work-related health problem experience					
Yes	12,5(4)	36,5(4)	8(3)	23,5(10)	82,25±12,40
No	13(3)	37(10)	8(1)	24(5)	80,11±11,63

Table 4. OHLS Analysis of Total Score and Scale Subfactors According to Participant Characteristics					
	Factor 1	Factor 2	Factor 3	Factor 4	OHLS Total
	X±SS /Median(IQR)[a]				
p	0,423	0,582	0,992	0,488	0,486
OHS Training Status					
Yes	13(2)	37(9)	8(2)	24(6)	80(16)
No	12(4)	36(10)	8(2)	23(3)	77,5(12)
p	0,007	0,381	0,845	0,216	0,753
Informing about Health Risks in the Department of Work					
Yes	13(2)	37(10)	8(2)	24(7)	81(16)
No	12(4)	35(8)	8(2)	23(5)	76(14)
p	0,000	0,019	0,169	0,007	0,002
Involvement in OHS Studies					
Yes	12,5(3)	34,5(8)	8,5(3)	23,5(5)	79,5(15)
No	13(3)	37(10)	8(2)	24(6)	80(16)
p	0,899	0,471	0,442	0,813	0,753
Status of pre-employment medical examination					
Yes	13(2)	36(10)	8(2)	23(7)	79(17)
No	13(3)	37(8)	8(5)	24(5)	81(13)
p	0,112	0,308	0,220	0,652	0,513
Status of periodic medical examination					
Yes	13(2)	37(9)	8(2)	24(6)	80(16)
No	12(4)	36(10)	8(1)	23(6)	78(14)
p	0,005	0,411	0,384	0,004	0,025
Department of Work					
Outpatient Clinic	12,5(2)	36,5(11)	8(2)	23(7)	79,35±10,56
Inpatient Ward	13(6)	34(9)	8(2)	23(7)	78,72±15,11
Emergency Room and Intensive Care Unit	14(2)	37,5(9)	8(3)	25(5)	78,07±11,47
Administrative Area	14(3)[c]	37(11)	8(3)	24(8)	82,75±12,43
Multiple Work Areas	12(3)[c]	36,5(8)	8(1)	23(4)	78,19±9,68
p	0,012	0,648	0,702	0,139	0,276

[a] If the groups conform to a normal distribution, the values are presented as X ± SS (mean ± standard deviation). If they do not follow a normal distribution, the values are presented as median value (IQR).
[b] The group that creates the difference.
[c] The groups that show significant differences in the post hoc analysis.

There is no study aimed to investigate OHS literacy among healthcare workers in Turkey. It is important that the Occupational Health Literacy Scale among healthcare workers.

In our study, the scores obtained from the sub-dimension of using and communicating OHS (Occupational Health and Safety) information were found to be higher in other healthcare workers compared to doctors. In a study related to

occupational accidents in the health sector, nurses (44%), doctors (28%), and technicians (15%) were the most exposed to injuries from sharp and piercing tools, due to representing the largest professional group in hospital workforce (12). In a study named "Occupational Accidents and Employee Safety in Hospitals" in 2013, it was found that 68% of nurses, 32% of doctors, and more than half of all staff had been exposed to injuries from sharp and piercing tools at least once in their working lives (13). Among healthcare workers, nurses are considered to be in the most at-risk group (14). According to these studies, the fact that other healthcare workers, most of whom are nurses, are exposed to occupational risks more than doctors may have resulted in them being more careful in terms of using and communicating OHS (Occupational Health and Safety) information. On the other hand, doctors' preference for curative health services over preventive health services may have led them to score lower in terms of using and communicating OHS information. After all, occupational health and safety is within preventive health services.

Actually, scores obtained by the employees in the PHC from the sub-dimension of accessing OHS information are lower compared to the employees of Provincial/District Health Directorates and State Hospitals; it can be interpreted as the employees thinking that PHC's are less risky in terms of OHS and do not need it, or the inadequacy of OHS trainings at the PHC level.

Participants with more years of work have higher scores in Total OHS Literacy, understanding OHS information, and using and communicating OHS information could be due to the increase in their experiences as the years of work increase. Only the scores obtained from the sub-dimension of accessing OHS information are higher in those who have received OHS training compared to those who have not, may be due to a deficiency in the content of OHS trainings or differences in the way individuals perceive the given trainings.

Participants who are informed about the health risks of the department they work in have higher scores in accessing OHS information, understanding OHS information, using and communicating OHS information, and total OHS Literacy, can be interpreted as providing specific risk information about the area they work in, leading to a clearer perception and importance of the subject in individuals.

Participants who have periodic examinations have higher scores in accessing OHS information, using and communicating OHS information, and total OHS Literacy, is an important finding in emphasizing the importance of periodic examinations. Essentiallt, participants working in the administrative field have higher scores from the sub-dimension of accessing OHS information compared to participants working in multiple fields, may be due to the personnel in administrative areas being responsible for receiving, organizing, being aware of, and following up on OHS trainings.

Limitations: The study utilized non-probability sampling, which resulted in a low representativeness of the sample for the population, leading to selection bias. Additionally, memory bias may have influenced participants' responses to certain questions (e.g., workplace accidents, pre-employment, and periodic medical examinations). The use of an online survey may have introduced information bias as participants could have misunderstood or misinterpreted the questions during completion.

CONCLUSION

Participants who have periodic examinations and are informed about health risks in the institution they work in have been found to have a higher total score on the occupational health literacy scale. It is recommended that health workers have regular periodic examinations at the institution they work in, that OHS trainings are planned for health workers, and that these trainings are repeated periodically. It is also important to encourage

doctors, who score lower than other health workers in the sub-dimension of using and communicating OHS information, to use and communicate OHS information to other health personnel, considering that their responsibilities are higher.

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Conflict of Interest

No conflict of interest

Support Resources

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Ethical Declaration

Ethical permission was obtained from the Cukurova University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 05.05.2023 and number 133, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: FİD, Aİ, HMS, TM, FT, HD, Design: FİD, Aİ, HMS, TM ,Supervising: FT, HD, Financing and equipment: FİD, Aİ, HMS, TM, Data collection and entry: FİD, Aİ, HMS, TM, Analysis and interpretation: FİD, Aİ, HMS, TM, Literature search: FİD,Aİ,HMS,TM

Writing: FİD, Aİ, HMS, TM, FT, HD Critical review: FİD, Aİ, HMS, TM, FT, HD

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INVITED REVIEW

Molecular Basis of Learning and Memory

Molecular Alterations in Learning and Memory

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Abstract:

As commonly known, learning is the process of acquiring a new information and memory is preservation of acquired information for later use. The difference in learning and memory capacities between different species and between different individuals of same species directed scientists to research the causes of this. According to commonly accepted approach these differences are due to the distinctions in synaptic alterations. In collaboration with advancing molecular techniques, the formation mechanisms of synaptic alterations, the reasons of differences between them, the changes that occur in neurons during learning and the changes that occur in neurons as a result of memory became popular research subjects nowadays. The researches that has been done are insufficient, however, many important findings are obtained until now. The changes that occur in pre-synaptic and post-synaptic neurons during simple non-associative learning, associative learning, short term memory and long term memory have been researched and different molecular mechanisms have been suggested.

Keywords: Non-Associative Learning, Associative Learning, Memory, Long Term Potentiation, Synaptic Plasticity

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INTRODUCTION

In the world of neuroscience, one of the most complex and fascinating mysteries is the process of learning and memory. From the first steps taken by a newborn baby to the vivid memory of valuable experiences in old age, the brain's ability to acquire, store and recall information is truly remarkable. Over the years, scientists have delved deeply into the neural underpinnings of this phenomenon, uncovering a complex molecular fabric that brings together the essence of learning and memory.

Although there are many different definitions of learning and memory made by different branches of science such as psychology, sociology, neurology, if we put these definitions together in the simplest form, learning is the act of acquiring new knowledge (or ability, behavior, preferences, values, etc.), and memory is the storage of this information permanently to be used later when necessary. The capacity to learn and remember what has been learned is the biggest feature that makes humans different from other living creatures. Just as there are differences in the capacity to learn and remember among different species, the fact that there are also differences between individuals of the same species has led scientists to search for the reasons that create these differences. Especially in recent years, with the advances in molecular techniques, previous neurology and psychology studies have gained a different dimension, and the molecular mechanisms that play a role in the ability to learn and remember have become an important research area.

Memory and learning were defined as a result of synaptic alterations by Hebb (1), who carried out very important studies in the field of neuropsychology. Today, although this idea is still accepted to some extent, it is argued that learning and memory are not only a result of these alterations, but that many mechanisms within neurons are also very important in these two events(2). Research on the second idea has generally intensified after the 1980s, and studies have been conducted on many different model organisms. Among these studies, Kandel and Schwartz (3) and Carew et al (4) can be considered the most important and pioneering ones. Due to its ability to perform specific forms of learning (habituation, sensitization, conditioning), the simplicity of its nervous system, the ease of deciphering its genetic structure, and the presence of large neurons, Aplysia californica (sea slug) is currently the most commonly chosen model organism in research on learning and memory(5).

Learning

Learning styles in living things can be divided into many subcategories such as non-associative learning, associative learning, imitation, learning by watching and listening, and learning through experience. Since most of these categories are the areas of interest of psychology and neurology, this article will focus on non-associative learning and associated learning, which are the basic learning styles on which molecular research focuses. The reason why molecular research focuses on these two subunits is that the results cover one or a few neurons and their results give an idea about the functioning of the entire system.

Non-Associative Learning

Non-associative learning can be defined as making an inference directly from a situation without directly associating it with another event(6). This learning form is examined in two subcategories: habituation and sensitization.

Habituation is the state in which the response in animals decreases as they are exposed to a repetitive stimulus for a certain period of time(7). It is a different form of integration. If an animal is exposed to a stimulus and reacts, but later realizes that this stimulus is not harmful or beneficial, it concludes that the stimulus is meaningless and its response gradually decreases with repeated stimuli, or its response may even stop completely. A simple example of this is the behavior of small birds. When these birds see a large predator bird placed in a cage, they reflexively start to run away. However, if the stimulus is repeated in the same way, it realizes that the predator cannot reach it and stops its reaction.

Sensitization is the sudden increase in the response to a repeated stimulus above the normal level or an increase in the response to the same stimulus after habituation, typically by changing the stimulus(7). Using the example given above, if the predator bird is released from its cage, the prey bird's response will be greater than usual because the stimulus has suddenly changed, catching the prey bird unprepared. Another example of sensitization could be a person rubbing his arm. The first reaction this person will give will be the same as the reaction he would give to the slight warmth he would feel. However, if the stimulus (rubbing) continues to be repeated, the warmth may start to be perceived as pain, leading to a change in the response.

These two simple forms of learning have been observed in all living things with a nervous system and have molecularly the same dynamics(8). Kandel and Schwartz (3) first explained the molecular mechanism and formation of these learning styles with their research. In their study, the behavior of Aplysia californica was examined. This organism has a structure called a siphon, and it possesses sensor neurons connected to this region (Figure 1)(9). These sensor neurons are linked to motor neurons that control the gill muscles. When the siphon is touched or stimulated, the interaction of these neurons results in the organism retracting its gill through a coordinated response (gill withdrawal reflex). In the conducted study, the contraction potential of the gill muscles was measured in response to the initial stimulation of the siphon and with an increasing number of stimuli. It was observed that this potential gradually decreased with each subsequent stimulation (habituation)(3). Following the habituation phase, the organism's head region was subjected to an electric shock, and then, when the siphon was touched, the contraction potential of the gill muscles was measured. Interestingly, it was observed that this potential was significantly higher than the normal potential (sensitization)(3). Following this stage, the question "What triggers these different responses?" arose, leading to an investigation of the changes occurring in neurons after habituation and sensitization. During the first and next few touches to the siphon, neurons generate action potentials in a normal manner. However, as the number of stimulation increases, calcium channels at the axon ends of pre-synaptic neurons (sensor neurons) are partially inactivated and the amount of neurotransmitter substance secreted to post-synaptic neurons (motor neurons) decreases. As the number of stimuli increases, more calcium channels become inactivated, resulting in a decrease in the response. Even when there is a break of several hours in touching the siphon, very little response is elicited from the organism upon subsequent stimulation(3). This has been considered as the simplest learning dynamic.

In the next phase of the study, an electric shock was given to the head area of the organism. It was found that this shock stimulated the third group of neurons seen in Figure 1 and triggered the release of serotonin from these neurons(3). As shown in Figure 2(10), it was found that the released serotonin subsequently triggered cAMP synthesis in sensor neurons, and cAMP activated protein kinases. The activated protein kinases then inhibited serotonin-sensitive potassium channels, reducing their activity. As a result, due to the potassium channels responsible for repolarization in neurons, the decreased activity leads to prolonged action potential duration. Consequently, it was concluded that the calcium channels at the axon terminals remained open for a longer duration, resulting in an increased release of neurotransmitter from sensor neurons(3). As one might predict, the increased neurotransmitter amount will lead to more stimulation in the post-synaptic region and confirm the observed situation. In many subsequent studies with different organisms, similar results have been found, and it is generally accepted that basic forms non-associative learning are consistent across various species(11).

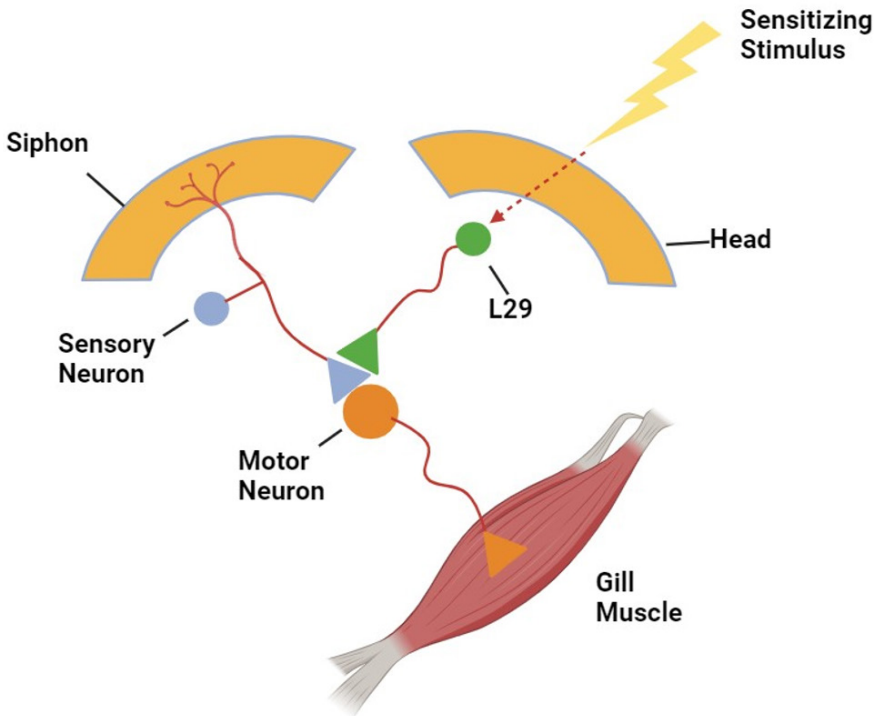

Figure 1. Representation of the nervous system of Aplysia California

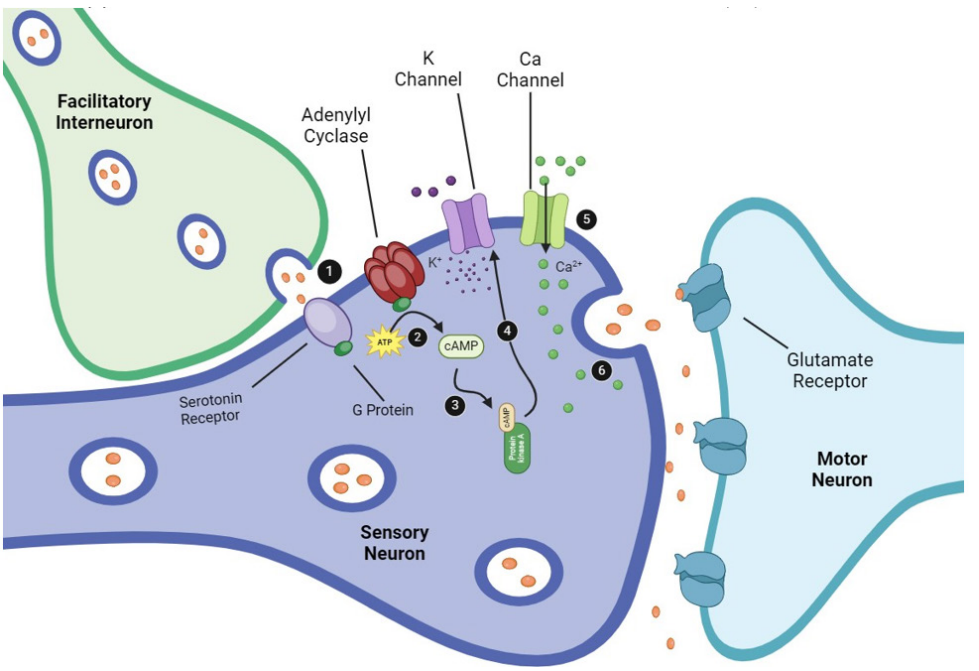

Figure 2. Short-term sensitization. **(1)** Binding of serotonin to G-Protein coupled receptor. **(2)** Stimulation of cAMP formation. **(3)** Binding of cAMP to the regulatory subunit of Protein Kinase A (PKA). **(4)** Catalytic subunits of PKA phosphorylate potassium channels. **(5)** Closing of potassium channels, prolongation of action potential duration, more calcium inflow. **(6)** More neurotransmitter release as a result of excess calcium(10).

In studies conducted in subsequent years, it has been frequently claimed that habituation and sensitization are not only short-term but also lead to long-term learning(12). Various research has been conducted on this subject. Dash et al (13) proposed, contrary to the mechanism described above that remains active for a short period, that for this simple form of learning to be long-lasting and transform into a kind of memory, some form of protein synthesis is necessary. In their research on this subject, they hypothesized that cAMP not only activates protein kinases but also binds to Cyclic AMP Response Element-Binding proteins (CREB). As it is known, CREBs perform functions that regulate transcription in the cell. The results of their research indicated that the activation of CREBs leads to changes in the number of potassium channels sensitive to various neurotransmitters and voltage-gated calcium channels. They have suggested that this plays a role in the permanence of learning(13). In subsequent similar studies, it was observed that organisms given CREB inhibitors during habituation or sensitization were unable to convert this short-term learning into long-term learning(14). This observation supported the idea that CREB plays a crucial role in the conversion of short-term into long-term learning.

Associative Learning

Associative learning can be categorized into classical conditioning and operant conditioning. Classical conditioning is defined as the triggering of one stimulus by another independent stimulus when they are perceived consecutively for a long time. It was first discovered by Ivan Pavlov as a result of his research on dogs.

Operant conditioning is the regulation of subsequent behaviors according to the consequences of a behavior. This concept was initially introduced by Edward L. Thorndike. The increased permanence of these two types of learning and the greater resemblance of the mechanisms influencing long-term memory compared to non-associative learning have intensified interest in this subject. Kandel (15) demonstrated that Aplysia californica can learn through classical conditioning and explained changes at the molecular level. In the conducted study, the snails were first subjected to an electric shock to the head region, followed by touching their siphon. As previously indicated, an increased response in the gill withdrawal reflex was observed compared to normal. A second group of Aplysia was not subjected to electric shock and served as the control group. It was found that, after a certain period the snails in the first group exhibited a heightened response when their siphon was touched even without receiving electric shock, compared to the control group. Furthermore, this heightened response could extend for up to 3-4 weeks depending on the frequency of electric shock application. Subsequently, the neurons leading to the sensor neuron from the head region of the snails that received electric shocks were destroyed, after which their siphon was touched. Surprisingly, it was measured that the organisms exhibited the same intensity of reflex(15). This led to the conclusion that the changes were not due to alterations in the neurons originating from the head region involved in conditioning, but rather resulted from changes in the neurons originating from the siphon. These changes were then investigated. It was found that repeated electric shocks increased serotonin release from neurons originating from the head region, leading to longer opening of calcium channels. However, with the continuous repetition of electric shocks, it was observed that the calcium levels in neurons increased significantly. Due to the excess calcium levels, some of the calcium binds to calmodulin. The resulting complex was observed to activate a type of adenylate cyclase called calcium-calmodulin-dependent adenylate cyclase, which is found exclusively in neurons. It has been suggested that instead of the short-lived activation via G-protein seen in classical sensitization, the stable structure of the calcium-calmodulin complex triggers the synthesis of cAMP in the cell for a prolonged period, thereby ensuring that the

conditioning is not forgotten for a certain period of time(15). This study, while not explaining situations where conditioning lasts for an extended period, has shed light on medium-term memory in organisms.

Memory

Memory is generally studied under two main categories: short-term and long-term memory. Short-term memory involves the immediate processing and evaluation of stimuli from sensory organs, followed by its rapid decay. The molecular dynamics of short-term memory are generally accepted to be similar to those of simple non-associative learning, as described earlier. Since necessary information about this topic has been provided above, this section will focus on long-term memory.

According to neuroscience, synaptic alterations form the basis of all memory, as mentioned earlier. These alterations include Long-Term Potentiation (LTP), Long-Term Depression (LTD), and Synaptic Plasticity (SP)(16). Briefly, LTP refers to the long-lasting and persistent enhancement of communication between two neurons that are continuously stimulated together. LTD, on the other hand, is the opposite, involving a long-lasting decrease in the connection between two neurons. SP encompasses the ability of synapses between two neurons to change their interaction depending on the current situation(16). While studies in neuroscience have revealed many findings about which brain regions are active during specific activities, they have not fully explained the reasons behind LTP, LTD, and SP occurring in different brain regions. To elucidate these reasons, numerous studies are ongoing, utilizing advancing molecular techniques. The aim of these studies is to uncover the molecular mechanisms underlying long-term learning and memory.

Two different perspectives have been proposed for molecular bases of these changes. The first one suggests that synaptic function changes as a result of modifications in synaptic proteins. Shi et al (17) found that N-methyl D-aspartate receptors (NMDAR) and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) in the postsynaptic neuron are activated by a type of protein kinase called continuous kinases. NMDAR and AMPAR are ionotropic glutamate receptors, and when glutamate binds to these receptors, they allow the entry of cations such as calcium, sodium, and potassium into the cell(10). According to their findings, an enzyme called ubiquitin hydrolase is produced in the postsynaptic neuron that is continuously stimulated together, and the amount of ubiquitin in the postsynaptic region is reduced in this way. Ubiquitin is known to mark proteins for degradation, and as a result of its decreased amount, the duration of activity of proteins in the postsynaptic region is prolonged. Consequently, continuous kinases emerge, and the activities and permeabilities of NMDAR and AMPAR change. When this situation persists, SP and LTP occur(17).

According to the second proposed model, the strength of the synapse between two neurons is dependent on the number of ion channels it possesses(18). In a dynamic state, NMDAR and AMPAR are continuously balanced through exocytosis and endocytosis. However, changes in synaptic activity between two neurons can shift this balance towards the addition or removal of new NMDAR and AMPAR, resulting in either LTP or LTD(19). Additionally, in LTP, it has been determined in various studies that these types of receptors outside the synaptic region are encouraged to undergo endocytosis by dynamin and clathrin and are subsequently transported to the synaptic region(20).

Hawkins et al (21) investigated the changes occurring in the presynaptic neuron during LTP and SP through their research. They suggested a model where a series of activations and protein syntheses work together and influence long-term memory. The proposed model resulting from this study is depicted in Figure 3(22).

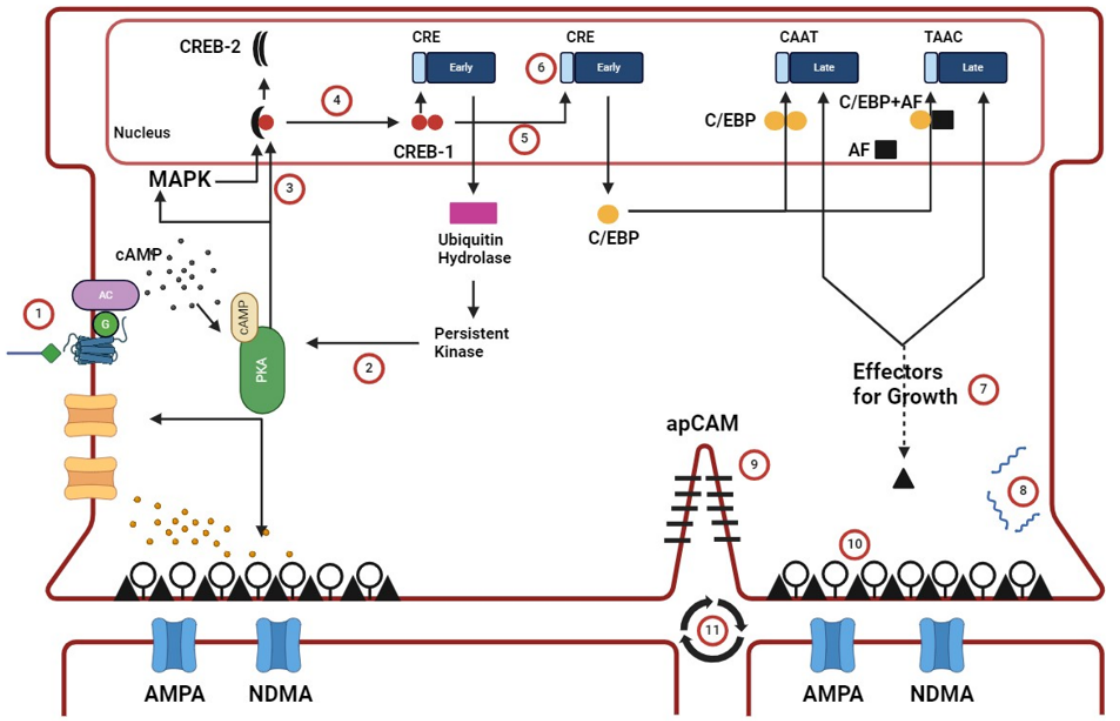

Figure 3. Changes in the pre-synaptic neuron in LTP and SP. **(1)** Short-term strengthening of synaptic connection as a result of neurotransmitters. **(2)** Balance of kinase and phosphatase activities at the synapse. **(3)** Retrograde transport from synapse to nucleus. **(4)** Activation of transcription factors. **(5)** Activity-dependent induction of gene expression. **(6)** Chromatin alteration and epigenetic changes. **(7)** Capture of newly synthesized products by synapses. **(8)** Stimulation of local protein synthesis in active synapses **(9)** Development of the synapse and formation of new synaptic regions. **(10)** Activation of pre-existing silent synaptic regions. **(11)** Stimulation of other nearby neurons by self-triggering molecular mechanisms(22).

In conclusion, studies on long-term memory have proposed various models, but there is no definitive consensus on how learned information is stored in the brain for extended periods or how it is recalled when needed. Many studies have found differences in learning and memory potential as a result of the stimulation or inhibition of various receptors or kinases with certain chemicals. However, these findings are still insufficient to explain how higher-level organisms perform complex brain activities such as memory recall, thinking, or learning from experiences.

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INVITED REVIEW

Current Developments in Small Cell Lung Cancer

SCLC treatments

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Abstract:

Small cell lung cancer (SCLC), often associated with smoking, is characterized by its aggressive biology and potential for early metastasis. It accounts for approximately 15% of all lung cancer patients. The combination of platinum-based chemotherapy and etoposide has been used for many years in the treatment of SCLC. The prognosis for patients with SCLC who are treated as a single group is still quite poor. Recent research has provided a new perspective on the biology of SCLC. A survival benefit has been demonstrated by adding immune checkpoint inhibitors to chemotherapy in patients with extensive stage SCLC.

The study of the molecular, biological, and immunological properties of the heterogeneous structure of SCLC is a promising area of research for the future. Identification of distinct gene expression profiles (ASCL1, NEUROD1, POU2F3, and YAP1) of SCLC patients may form the basis of the most effective and individualized therapeutic treatments in disease management. More research is needed to identify SCLC subtypes and develop effective treatments for this group of patients who have a poor prognosis.

Keywords: Small cell lung cancer, treatment, gene expression

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INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15 percent of all lung cancer cases (1). Almost all SCLC patients are related to smoking (2). SCLC is characterized by rapid proliferation, high growth fraction, and early metastasis development (3). More than two-thirds of SCLC patients are diagnosed in an advanced stage. The combination of platinum-based chemotherapy (carboplatin or cisplatin) with etoposide has been used in the treatment of SCLC for years and continues to form the backbone of modern combination methods (4). Although this treatment initially works well for most patients, many relapse in a short time. The 5-year survival rate in SCLC patients with poor prognosis is less than 7% (3). Compared to other types of lung cancer, personalized treatment for SCLC patients is limited, resulting in poor prognosis. The disease appears homogeneous. However, new studies show that immunotherapy is clinically effective in treating advanced SCLC (5).

The Genetic Structure Of Small Cell Lung Cancer

In the whole-genome analysis performed to identify somatic driver mutations that play a key role in the development of SCLC, it was determined that the tumor suppressor genes TP53 and RB1 were inactivated (6). In a study of 110 SCLC patients, almost all of the tumors showed bi-allelic inactivation of TP53 and RB1 genes (7).

Notch signaling is crucial in the development of neuroendocrine cells and is considered a tumor suppressor in Small Cell Lung Cancer (SCLC). Mutations in genes belonging to the Notch family have been found in about 25% of human SCLC cells. In a preclinical mouse model, the activation of Notch signaling was found to significantly reduce the tumor growth rate and prolong the survival of the mutant animal (7). Comprehensive genomic analyses have detected amplifications of several genes in Small Cell Lung Cancer (SCLC). The amplification of all MYC family members (16%), FGFR1 (6%), and SOX2 (27%) have been found. SOX2, which is a transcriptional regulator for pluripotent stem cells, is usually overexpressed, particularly in the SCLC-A subtype. It is also believed that MYC amplification occurs during tumor growth and is associated with treatment resistance. Aurora kinase A and B (AURK A/B) are serine/threonine kinases that regulate mitosis. Preclinical investigations have shown the effectiveness of AURK A/B inhibitors in treating SCLC (9).

Subtype Classification In Small Cell Lung Cancer

Although SCLC is still clinically treated as a single disease, recent preclinical research has found biologically distinct SCLC subtypes. In the 1980s, cancers were classified solely by their dominant phenotype, namely “classic” and “variant” (7). NE-high and NE-low subgroups were identified and classified based on the expression patterns of various neuroendocrine markers, such as chromogranin A (CHGA), synaptophysin (SYP), neural cell adhesion molecule 1 (NCAM1/CD56), and gastrin-releasing peptide (GRP) (8). Recent studies have shown that the traditional categories used to classify small cell lung cancer (SCLC) have limited effectiveness in determining a course of treatment. However, with the help of genomics and new preclinical models, researchers have been able to study the intratumoral heterogeneity and genetic changes of this disease more effectively. As a result, a new subtype of SCLC has been identified, which is characterized by differential expression patterns. The identification of this subtype was based on extensive data from studies involving human SCLC cell lines, genetically engineered mouse models, and patient-derived xenografts. These studies have suggested the involvement of four key transcriptional regulators: ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P), as well as inflammatory markers (SCLC-I) (Figure 1) (9). This novel classification of SCLC is based on various molecular profiles and neuroendocrine markers, which correlate with different clinicopathological features. It is particularly useful for prognostic and predictive

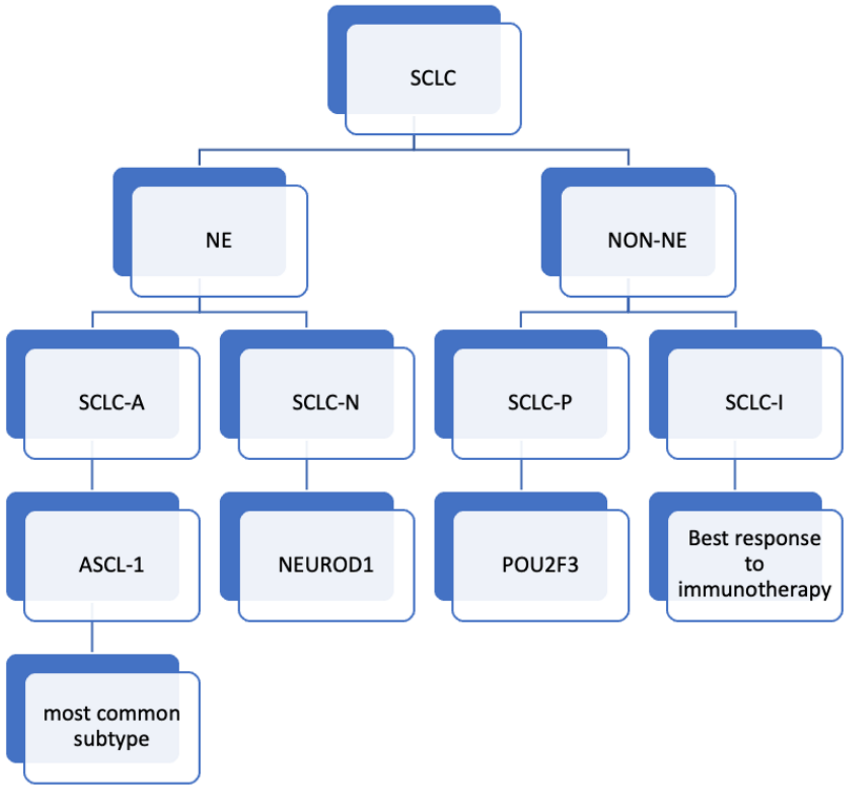

Figure 1: Neuroendocrine differentiation and molecular subtypes of SCLC

purposes (5).

SCLC, small cell lung cancer; NE, neuroendocrine; ASCL1, achaete-scute homologue 1; INSM1, insulinoma-associated protein 1; NE, neuroendocrine; NeuroD1, neurogenic differentiation factor 1; POU2F3, POU class 2 homeobox 3.

SCLC-A

SCLC-A is the most common subtype of SCLC, accounting for 40-50% of all cases. It has a classical morphology and expresses a high number of neuroendocrine markers (4). Typically, Small Cell Lung Cancer subtype A is characterized by an increase in BCL-2, EZH, DLL3, SOX2, INSM1 amplification, and a decrease in CREBBP level (5). "BCL-2" is a cellular signaling molecule that prevents cell death. It is directly controlled by the ASCL1 gene, which regulates its transcription (4). In preclinical models of small cell lung cancer (SCLC), venetoclax, a BCL2 inhibitor, has been demonstrated to cause tumor regression (5) . The molecule DLL3 is a ligand for the Notch pathway and is an interesting target for treatment. Around 85% of small cell lung cancer (SCLC) cells have DLL3 expressed on their surface. An antibody-drug conjugate called rovalipatumab (Rova-T) has been developed to target DLL3 and has been tested on patients with SCLC that express DLL3 in the TRINITY phase 2 trial. The results have shown that the treatment has had a positive clinical response in patients who had received third-line or higher treatment (10). However, a phase 3 randomized controlled trial failed to demonstrate superiority over topotecan in second-line treatment (11).

Tarlatamab is a bispecific molecule that binds to two different proteins in cancer cells and T cells, respectively. By doing so, it activates T cells to attack and destroy cancer cells. In a phase 1 clinical trial, Tarlatamab showed promising results in treating small cell lung cancer (SCLC) that had previously been treated. The median duration of response

(mDoR) was 12.3 months, and the median overall survival (mOS) was 13.2 months. These results suggest that Tarlatamab has exceptional efficacy in treating SCLC and warrants further investigation (12). Due to the inactivation of CREBBP, SCLC-A subtype exhibits higher sensitivity to histone deacetylase (HDAC) inhibitors (4).

SCLC-N

The SCLC-N subtype is defined by the transcription factor NEUROD1, characterized by low expression of neuroendocrine markers, c-Myc amplification, increased aurora kinase (AURK) activity, and arginine biosynthesis (4). It was observed that a combination of small cell lung cancer with both neuroendocrine and non-neuroendocrine histology (SCLC-A and SCLC-N) was also identified (5).

SCLC-P

POU2F3 is a transcription factor that regulates tuft cells. The SCLC-P subtype may have originated from tuft cells due to high POU2F3 expression (13). Patients with this subtype lack neuroendocrine markers. Targeted treatment options may include nucleoside analogs, PARP inhibitors, and IGF-1R inhibitors (5).

SCLC-I

Expression of YES-associated protein (YAP) 1 was used to define the subtype SCLC-Y, which was initially proposed but not confirmed as a distinct type in human samples (5). PD-1 and PD-L1 expressions are not unique to the SCLC-Y subtype. However, YAP1 has been shown to create an immunosuppressive environment that increases PD-L1 transcripts. SCLC-Y tumor cells express both LAG-3 and CD38, making them more responsive to immune checkpoint inhibitors. Moreover, the SCLC-Y subtype is particularly sensitive to polo-like kinase (PLK), mammalian target of rapamycin (mTOR) and possibly cyclin-dependent kinase (CDK) 4/6 inhibitors (5).

It has been predicted that samples lacking significant expression of ASCL1, NEUROD1, POU2F3, or YAP1 would be classified as a quadruple negative subtype of small cell lung cancer (SCLC-QN). To determine whether this SCLC-QN subtype is comparable to the SCLC-I subtype, which is quadruple switch-transcription factor negative but exhibits inflammatory characteristics, further investigation is required. It has been observed that the SCLC-I subtype has a high response to immune therapy due to its high infiltration of cytotoxic T cells, natural killer cells, and tumor-associated macrophages, as well as its high expression of various immune checkpoint markers (5).

Staging in small cell lung cancer

Two different staging systems have been presented for small cell lung cancer: the Veterans Administration Lung Study Group (VALG) classification and the tumor-node-metastasis (TNM) staging system. The VALG classification defines an extensive stage (ES-SCLC) as disease beyond the ipsilateral hemithorax, such as malignant pleural/pericardial effusion or hematogenous metastases. On the other hand, a limited stage (LS-SCLC) describes disease that is contained within the ipsilateral hemithorax and can be safely treated within a radiation field (14). The National Comprehensive Cancer Network (NCCN) and other clinical guidelines consider TNM stages I-III as LS-SCLC and stage IV as ES-SCLC.

Strategies for treating small cell lung cancer in its limited stage (LS-SCLC)

The standard systemic therapy for LS-SCLC patients is a combination of etoposide and platinum. The use of radiation and chemotherapy together has been shown to improve local control and increase survival rates. At present, there is insufficient data to support the use of immunotherapy for LS-SCLC (1).

Treatment approaches in extensive stage small cell lung cancer (ES-SCLC)

For several years, the main treatment for ES-SCLC has been a combination of platinum-based chemotherapy (carboplatin or cisplatin) and etoposide. A recent study has shown that the use of immune checkpoint inhibitors alongside chemotherapy can improve the

survival rate of patients with ES-SCLC. Atezolizumab is a monoclonal antibody that blocks PD-L1's interaction with PD-1 and B7.1. The IMpower133 study was a phase III, double-blind, randomized controlled trial that investigated the effectiveness and safety of adding atezolizumab or placebo to first-line carboplatin and etoposide treatment in patients with extensive-stage small-cell lung cancer (ES-SCLC). The study found that the overall survival (OS) was 12.3 months for the chemotherapy + atezolizumab group and 10.3 months for the chemotherapy alone group (hazard ratio [HR] for death, 0.70; 95% CI, 0.54-0.91; P =0.007) at a median follow-up of 13.9 months. The atezolizumab plus chemotherapy arm showed a median progression-free survival (PFS) of 5.2 months, whereas the chemotherapy alone arm had a PFS of 4.3 months (HR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02) (Table 1). In the group of patients who received a combination of atezolizumab and chemotherapy, 34.0% of them were still alive after 18 months. On the other hand, in the group of patients who were given a placebo along with chemotherapy, only 21.0% were still alive. The study showed that adding atezolizumab to chemotherapy was beneficial for patients, regardless of whether they had TMB or PD-L1 immunohistochemistry. In both therapy groups, a similar percentage of patients experienced adverse events (94.9% and 92.3%, respectively). Among the patients, 48 out of 196 (24.5%) in the placebo group and 79 out of 198 (39.9%) in the atezolizumab group developed immune-mediated adverse events. The study did not allow thoracic radiation therapy during the maintenance period, but prophylactic cerebral irradiation was allowed. After receiving treatment for brain metastases, there were no statistically significant differences in overall survival or progression-free survival between the two groups. However, due to the limited number of patients with brain metastases who participated in the study and the exploratory nature of the analysis, it is not possible to draw any definitive conclusions (15). The role of immunotherapy in small cell lung cancer patients with brain metastases requires further research.

Durvalumab is another type of immunotherapeutic treatment that has been proven to be effective in treating ES-SCLC. It is a human IgG1 monoclonal antibody that is selective and high-affinity, which prevents PD-L1 from binding to PD-1 and CD80. The safety and effectiveness of durvalumab in combination with etoposide plus cisplatin or carboplatin, with or without tremelimumab, for first-line therapy of patients with ES-SCLC were evaluated in the double-blind, randomized controlled, phase III CASPIAN study. Durvalumab plus platinum-etoposide resulted in a median overall survival of 13.0 months (95% CI 11.5-14.8), compared to 10.3 months (9.3-11.2%) in the platinum-etoposide group (HR, 0.73; 95% CI 0.59–0.91; p=0.0047) (Table 1). It was found that there is a significant difference in overall survival between the two groups of patients. All subgroups of patients showed an improvement in overall survival. Out of the 266 patients who received platinum-etoposide plus durvalumab, 62% (166 patients) experienced grade 3 or 4 any-cause adverse events. Similarly, out of the 265 patients who received durvalumab, 62% (163 patients) experienced grade 3 or 4 any-cause adverse events. Additionally, 5% (13 patients) and 6% (15 patients) experienced adverse events that resulted in death.(16).

Table 1: Treatments For First Line Extensive Stage Small Cell Lung Cancer

Trial	**Treatment**	**mPFS** (months)	**mOS** (months)
IMpower133	Carboplatin+Etoposid+ Atezolizumab Carboplatin+Etoposid+Placebo	5,2 (HR:0,77; P : 0,02) 4,3	12,3 (HR:0.70; P :0.007) 10,3
CASPIAN	Cisplatin/Carboplatin+Etoposid+Durvalumab Cisplatin/Carboplatin+Etoposid+Placebo	5,1 (HR: 0,78) 4,9	13,0 (HR, 0,73;p:0.0047) 10,3

HR, hazard ratio; OS, overall survival; PFS, Progression-free survival

Adding durvalumab or atezolizumab to the platinum and etoposide combination is the current first-line treatment for ES-SCLC patients with available data.

Although SCLC patients usually respond well to first-line treatment, many of them tend to relapse. Patients who experience a relapse within three months of receiving the initial treatment are considered "refractory" and require a different treatment regimen. On the other hand, patients who experience a recurrence more than six months after the first-line treatment are referred to as "sensitive" and can be treated again with the same regimen (1). Unfortunately, the response rate in subsequent treatment steps after the initial line of treatment is reduced, and the prognosis is poor (17).

Topotecan is the only approved second-line treatment for SCLC. Prior to its discovery, anthracycline-based regimens such as CAV (cyclophosphamide-doxorubicin-vincristine) were commonly used (18). In the randomized study comparing topotecan with CAV, topotecan was found to be as effective as CAV while presenting fewer grade 4 neutropenia side effects and better symptom control (19).

Lurbinectedin, a new alkylating drug that inhibits oncogenic transcription, has been approved as a second-line therapy for metastatic SCLC patients (20). Additionally, ongoing studies are being conducted to identify new therapeutic targets and develop more effective treatment plans.

CONCLUSION

Recent research has provided a new perspective on the biology of SCLC. This cancer type is heterogeneous in structure, so ongoing research is being conducted to evaluate its molecular, biological, and immunological characteristics. By identifying distinct gene expression profiles (ASCL1, NEUROD1, POU2F3, and YAP1) of SCLC patients, the most effective and individualized therapeutic treatments can be developed for disease management. However, more study is required to understand the subgroups of SCLC. As this patient population has a very poor prognosis, it is essential to develop effective novel treatments.

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