

# GEORGIAN MEDICAL NEWS

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии  
საქართველოს სამედიცინო სიახლენი

## GEORGIAN MEDICAL NEWS

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**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

**GMN: Медицинские новости Грузии** - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

**GMN: Georgian Medical News** – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

### WEBSITE

[www.geomednews.com](http://www.geomednews.com)

## К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html) В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

**При нарушении указанных правил статьи не рассматриваются.**

## REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html)  
[http://www.icmje.org/urm\\_full.pdf](http://www.icmje.org/urm_full.pdf)

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned  
Requirements are not Assigned to be Reviewed.**

## ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალებების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

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## ESTIMATION OF SERUM FERROPORTIN AND LIVER ENZYMES IN BREAST CANCER PATIENTS

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### Abstract.

Breast cancer (BC) is a common malignancy and a major cause of death in women. We sought to evaluate ferroportin plasma concentration in patients with BC. A total of 90 subjects (60 BC versus 30 control healthy) enrolled in the present study. Blood sample withdrawn and serum separated for measurement of total serum bilirubin (TSB), Aspartate Transaminase (AST), alanine transaminase (ALT), ferroportin (FPN). Results: A non-significant ( $p < 0.852$ ) differences exists between the level TSB in BC group ( $0.665 \pm 0.365$ ) compared to control group ( $0.654 \pm 0.191$  mg/dl). AST in BC group ( $40.1 \pm 36.0$ ) has shown a highly significant ( $p > 0.001$ ) difference comparing with the control group ( $22.5 \pm 14.2$  U/L). ALT in BC group ( $29.7 \pm 26.7$ ) has shown a highly significant ( $p > 0.004$ ) difference comparing with the control group ( $18.19 \pm 9.51$  U/L). FPN (ng/mL) in BC group ( $2.47 \pm 1.59$ ) has shown a highly significant ( $p > 0.002$ ) difference comparing with the control group ( $4.44 \pm 1.20$ ). Conclusion: the study concluded that breast cancer was associated with elevated AST, and ALT with reduced FPN and no changes reported with TSB levels.

**Key words.** Breast cancer, serum bilirubin, Aspartate Transaminase, alanine transaminase, Ferroportin.

### Introduction.

Cancer is characterized by loss of control of cellular growth and development leading to excessive proliferation and spread of cells [1-4]. Breast cancer (BC) is the most common term for a set of breast tumor subtypes with distinct molecular and cellular origins and clinical behavior. Most of them are the origin of ductal or lobular epithelial tumors. Breast cancer starts when cells in the breast begin to grow out of control and the capacity of these cells to infiltrate and invade natural tissue locally. These cells usually form a tumor that can often be seen on an x-ray or felt as a lump. Breast tumors could be classified into benign and malignant tumor (cancerous) [5-8].

Iron is an essential nutrient that is involved for many cellular processes, including electron transport chain (ETC), citric acid cycle, heme synthesis, and the cofactor of DNA Polymerase. Extra metabolic iron is stored in the form of ferritin and hemosiderin in the reticuloendothelial system mainly in the liver and macrophage of the spleen [4]. In order to maintain sufficient and healthy iron level in the body, cells require the coordination of a wide range of genetic activities, which are tightly regulated by both intracellular (via iron response element (IRE)/iron regulatory protein (IRP) regulatory pathway) and systemic iron metabolism (Hepcidin / Ferroportin) [7]

Ferroportin (ferroportin 1, also termed Ireg1, MTP1, and SLC40A1) is a cell surface transmembrane protein and is the only known export protein for nonheme iron. Ferroportin is expressed at high concentrations on duodenal enterocytes, placenta, hepatocytes, and macrophages and is an essential component

of systemic iron homeostasis that play a critical determinant of outcome in breast cancer, ferroportin concentration was found to be low in the breast tumors [8].

The liver is one of the largest organs in the body, and it performs an amazing array of vital functions in the body's maintenance, performance, and regulation of homeostasis. Serum measurements of liver-derived enzymes, non-enzymatic proteins, and metabolites of liver metabolism (collectively known as liver function tests (LFTs)). The standardized batch of LFTs usually comprises alanine aminotransferase (ALT; and sometimes, aspartate aminotransferase (AST), alkaline phosphatase (ALP),  $\gamma$ -glutamyltransferase (GGT), and other non-enzymatic proteins (e.g., albumin) and metabolites of heme metabolites, such as bilirubin [9-11].

The main purpose of the present study was to evaluate ferroportin and liver enzymes in patients with BC and control subjects.

### Materials and methods.

This study has investigated 90 women (60 patients and 30 controls), their ages between (30-70) years. The patients were referred to three main facilities, Kirkuk oncology center, consultation of early detection of breast tumor in Azadi hospital, and Kirkuk general hospital from November 2022 to March 2023.

About 5 ml venous blood was collected from each case by using a sterile disposable syringe then unloaded into gel tubes and allowed to clot at room temperature for 20 minutes. All samples were centrifuged at 3000 rpm for 15 minutes; sera removed and divided into four Eppendorf tubes 500  $\mu$ l for each sample, then stored at - 30 C until used to the time of biochemical assay.

An enzyme-linked immune sorbent assay (ELISA) was used to determine concentrations of ferroportin. Serum AST, ALT, ALP, and Total Serum Bilirubin (TSB) levels were measured by spectrophotometric kit.

Statistical analysis: All data were analyzed by using the Minitab program according to the ANOVA test. However, the mean when compromised by t T-Test under the P. value 0.05.

### Results.

The total number of a subject that participate are 90 (60 patient and 30 control) This study showed that the peak age of women with breast cancer was between 45 – 56 years and its percentage was 40%, while the least age group 35-44 years and its percentage which was found to be 27 % (table 1).

As shown in table (2), the mean of the serum level of total serum bilirubin (TSB) in breast cancer women comparing with the control group ( $0.665 \pm 0.365$  versus  $0.654 \pm 0.191$  mg/dl). The result was non-significant ( $p < 0.852$ ).

As shown in table (3), the mean of the serum level of AST in breast cancer women comparing with the control group ( $40.1 \pm 36.0$  versus  $22.5 \pm 14.2$  U/L). The result was highly significant ( $p > 0.001$ ).



**Table 1.** Relation the number of breast cancer women with Age.

Age group(years)	NO.	%
35-44	16	27
45-56	24	40
55-76	20	33
Total	60	100%

**Table 2.** Serum level of TSB in women with breast cancer versus control group.

Study groups	No.	TSB (mg/dL)	p value
Breast cancer women	60	0.665 ± 0.365	0.852
Control group	30	0.654 ± 0.191	

**Table 3.** Serum level of AST in women with breast cancer versus control group.

Study groups	No.	AST (U/L)	p value
Breast cancer women	60	40.1 ± 36.0	0.001
Control group	30	22.5 ± 14.2	

**Table 4.** Serum Level of ALT in women with breast Cancer versus control group.

Study groups	No.	ALT (U/L)	p value
Breast cancer women	60	29.7 ± 26.7	0.004
Control group	30	18.19 ± 9.51	

**Table 5.** Comparison between concentration of ferroportin breast cancer versus control group.

Study groups	No.	Ferroportin (ng/mL)	P. value
Breast cancer women	60	2.47 ± 1.59	0.002
Control group	30	4.44 ± 1.20	

**Table 6.** Correlation of TSB, AST, and ALT with the stage of disease breast cancer women.

Breast cancer women	TSB	AST	ALT
G1 (N.14)	0.611a ± 0.404	60.70a ± 6.80	32.99a ± 34.20
G2 (N.22)	0.638a ± 0.261	30.95bc ± 4.83	25ab ± 16.50
G3 (N.16)	0.654a ± 0.416	35.88b ± 5.02	30a ± 34.81
G-M (N.8)	0.832a ± 0.440	38.22b ± 3.81	26.13ab ± 15.81
Control (N.30)	0.654a ± 0.191	22.53c ± 4.24	18.19b ± 9.51
P-Value	0.548	0.004	0.0027

**Table 7.** Relation of Ferroportin with the stage of disease breast cancer women.

Breast cancer women	Ferroportin
G1 (N.14)	3.936a ± 1.432
G2 (N.22)	3.301a ± 1.236
G3 (N.16)	3.259a ± 1.095
G-M (N.8)	3.397a ± 1.101
Control (N.30)	3.440a ± 1.198
P-Value	0.192

As shown in table (4), the mean of the serum level of ALT in breast cancer women comparing with the control group (29.7 ± 26.7 versus 18.19 ± 9.51 U/L). The result was highly significant (p > 0.004).

As shown in table (5), the mean of the serum level of Ferroportin in breast cancer women comparing with the control

group (2.47 ± 1.59 versus 4.44 ± 1.20 ng/mL). The result was highly significant (p > 0.002).

The result of TSB level was no significant difference p-value 0.548 between G1, G2, G3 and G-M (0.611a ± 0.404, 0.638a ± 0.261, 0.654a ± 0.416 and 0.832a ± 0.440), respectively compared with control group (0.654a ± 0.191).

The result of A S T level was significant difference p-value 0.004 between G1, G2, G3 and G-M (60.70a ± 6.80, 30.95bc ± 4.83, 35.88b ± 5.02, and 38.22b ± 3.81), respectively compared with control group (22.53c ± 4.24).

As regards the result of A L T level was significant difference p-value 0.0027 between G1, G2, G3 and G-M (32.99a ± 34.2, 25ab ± 16.5, 30a ± 34.81, and 26.13ab ± 15.81), respectively compared with control group (18.19b ± 9.51) (Table 6).

The result of Ferroportin level was no significant difference p-value 0.192 between G1, G2, G3 and G-M (3.936a ± 1.432, 3.301a ± 1.236, 3.259a ± 1.095, 3.397a ± 1.101), respectively compared with control group (3.440a ± 1.198) (Table 7).

## Discussion.

This study reveals that, the highest rate of breast cancer in women was within the age group 45 – 56 years and the least was within the age group of 35-44 years. Numerous results obtained by other studies were focused on the age of women with breast cancer, e.g., the study that carried by Ghanim H et al, [12] who found that the mean age of breast cancer women was (42.2 ± 10.41) years, while the study by Armstrong K [13]. Who found that the mean age was (50.4 ± 12.45) years with range of 22 to 80 years. In United Kingdom, where the age standardized incidence for the breast cancer among women aged between 50 to 60 years, may be due to the familial and the hormonal factors [14]. As shown in figure (1) that on distributing cases according to age it was seen that most malignant cases were in aged group 45 – 56 years of age group (i.e. 40%), while no cases was observed < 23 years of age group, this results are similar to study in breast cancer by Mac Mahon B et al. [15] were in 40 – 49 years of age (i.e. 52.5%), and there were no cases in < 23 years of age, while the findings were observed by Navneet Kaur A [16], that the maximum number of cases of carcinoma of breast were in the age group of 35 to 44 years. Previous study done in Khalid found similar finding and agree with the present study [17].

The mean distribution of TSB serum levels for studied groups are listed in tables (2). Total bilirubin concentration reflects the liver's functional transport capability and has strong antioxidant effects. This might be attributed to lower hepatocyte damage and no increase in haemoglobin breakdown in BC patients. The production of apolipoprotein D by unconjugated bilirubin reduced BC cell line proliferation in a dose-dependent way, which might explain the small decrease of bilirubin reported in BC patients with high triglyceride levels in an attempt to minimize BC cell growth [18]. This study showed insignificant change in TSB concentration and our results in agreement with Albdusallam et al. [19]. that was observed an insignificant change in the levels of TSB. The study was done by Nwozo et al., also reported that TSB was a non-significant decrease in the bilirubin level when compared with control. Despite taking a group of patients on chemotherapy/radiotherapy and immune booster supplements (a combination of essential vitamins and

minerals), this study agreed with it. Because, following surgery, most cancer patients receive a combination of radiation and/or chemotherapy, which might increase oxidative stress [20].

The current study assessed the serum biochemical profile (AST) of BC patients undergoing RT. RT may change the levels of biological components in the blood, influencing organ systems. Serum biochemical marker can assist evaluate disease progression, metastasis, and therapy options for breast cancer. The liver enzyme (AST) in this study shows highly significant changes, which mean the radiotherapy affected liver.

In this study, there is significant increase in AST level in the breast cancer patients when comparing with healthy subjects. This was in agreement with Said (2019) study [21]. While Alkindi and Alhashemi (2022) study, who reported AST levels study did not show any significant changes  $p < 0.528$ , which mean the radiotherapy does not affect liver in cases of breast cancer patients than healthy controls [22].

The study of Nwozo, et.al informed that breast cancer patient compared with the control, There was a significant increase ( $p < 0.05$ ) in AST activity [20]. AST plasma activity is the most often utilized indicators of hepatocellular injury, as they are intracellular enzymes that are released into the blood following cellular damage. AST is found in the heart, brain, kidney, and skeletal muscles, making it less selective for liver damage. Their plasma activity rises as a result of damage to and leaking through the cellular membrane. In breast cancer patients, the increased AST activity in the breast cancer patient might be a result of inflammation or injury to other organs, or it could be a result of cancer metastasizing to other organs in the body [23].

The present study shows an increase in the serum AST in breast cancer women comparing with the control group, these results were in congruence with Sathesh et al. who showed that chemotherapeutic drugs administration cause tissue damage and an increase of enzymes membrane leakage of these enzymes [24]. Also, the present study was in agreement with Damodar et al. who revealed that the incidence of hepatotoxicity in patients treated with chemotherapeutic drugs [25]. Anber et al. stated that about 40% of patients suffered liver damage after doxorubicin treatment [26]. This was supported with a study by Llesuy and Arnaiz who stated that doxorubicin administration produced increases of 51% and 53% in liver spontaneous chemiluminescence and malonaldehyde formation; respectively. The main characteristics of these processes were elevations in serum levels of ALT, AST, and bilirubin [27]. The underlying mechanism is that doxorubicin causes an increase in the Malondialdehyde levels together with a decrease in the serum levels of superoxide dismutase and catalase activity through the one-electron reduction of nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P-450 reductase enzyme [27]. Previous studies reported that administration of antioxidants such as vitamin E, C, and A could reduce the hepatotoxic effect of doxorubicin. And that both virgin olive oil and selenium could be given as dietary supplements with the appropriate concentration and dosage form to maximize the antitumor action of these agents and to minimize the hepatotoxic effect of doxorubicin. Chauhan et al. found that the levels of these enzymes were increased but still within the normal

reference ranges during the different courses of chemotherapy this was explained by the progressive liver damage caused by the chemotherapeutic drugs [28].

We detected that serum levels of ferroportin were significantly lower in breast cancer patients than the controls. After radiotherapy, its level decreased significantly in patients versus pre radiotherapy. This highlights the impact of radiation on ferroptosis. Silencing ferroportin increases the cellular labile iron pool and lipid peroxidation, thereby sensitizing cells towards ferroptosis [29,30]. Geng et al. [31] found knockdown of ferroportin accelerated erastin-induced ferroptosis by increasing iron-dependent lipid ROS accumulation, highlighting ferroportin as a potential therapeutic target site for neuroblastoma. Our study agreement with Ali et al., [32] reported that serum ferroportin levels were significantly lowered in breast cancer compared to control ( $0.589 \pm 0.107$  vs  $1.37 \pm 0.28$  ng/ml respectively). The metabolism of iron is closely regulated by hepcidin which is liver-derived peptide. It exerts its action by interacting with a ferroportin (FPN), a transmembrane protein implicated in iron efflux from the body iron stores. Binding of hepcidin with FPN exerts a negative effect on erythropoiesis by inducing internalization and then subsequently destruction of FPN [32].

Inoguchi et al. [33] Breast cancer risk also tended to be associated with high bilirubin levels ( $\geq 0.9$  mg/dL) ( $P = 0.144$ ) No significant association was found between serum bilirubin levels and breast cancer in all stages risk in women Serum bilirubin levels are influenced by many environmental factors, including physiological and pathological conditions, as well as genetic factors. In addition, low bilirubin levels have been reported in patients with various chronic diseases and conditions, such as diabetes, obesity, aging-related disability [32,33]. Therefore, the association between low bilirubin levels and cancer risk may be mediated, at least in part, by the effect of these factors. However, the present study revealed that the association remained significant even after the model was adjusted for these variables. Taken together, low bilirubin levels may reflect a total susceptibility determined by both genetics and various environmental factors to some types of cancers, and thus might be a clinically useful biomarker for the risk of cancer development. Serum bilirubin levels are highly related to genetics, and many genome-wide association studies have shown the substantial contribution of various UGT1A1 polymorphisms to human serum bilirubin levels [33]. Serum estrogen activities are also regulated by UGT1A1 by the conjugation and subsequent direct inactivation of estrogens<sup>32</sup>. Therefore, it is very likely that high bilirubin levels due to UGT1A1 polymorphisms may be accompanied by high activities of serum estrogens and a subsequently increased risk of estrogen-dependent cancers. In fact, several studies have shown that increased estrogen activities due to UGT1A1 polymorphisms may be associated with an increased risk of breast cancer [34].

O'Malley et al. [35] reported that liver function tests did not demonstrate significant differences in G1 stage of disease breast cancer women ALT:  $25.47 \pm 10.55$  vs  $21.54 \pm 8.03$  U/L and AST:  $25.75 \pm 10.72$  vs  $24.58 \pm 6.93$  U/L. In the G2 group, ALT and AST demonstrated a statistically significant increase from baseline

to 6 months ( $P<0.05$ ), liver function tests did not demonstrate statistically significant changes from 6 months to 12 months in all stages of disease breast cancer women.

Chemotherapy is an effective drug which has been widely used for the treatment of hormone receptor-positive breast cancer. Women taking tamoxifen from 5 to 10 years exhibit the reduction of the risks of breast cancer recurrence and mortality. While generally well-tolerated, Chemotherapy is known to induce fatty liver in 43% of women within the first 2 years of treatment. Moreover, the incidence of Chemotherapy induced abnormal ALT, AST was estimated to be around 40% at 1 year [36,37].

### Conclusion.

Breast cancer is one of the most common types of cancer that affects women globally. It is a complex disease that involves the uncontrolled growth of abnormal cells in the breast tissue. Researchers have been working tirelessly to identify potential biomarkers that can aid in the early detection and diagnosis of breast cancer. One such biomarker is ferroportin, which is a transmembrane protein that transports iron out of cells. Recent studies have shown that there is a significant difference in the serum level of ferroportin in breast cancer women as compared to the control group. The study conducted on ferroportin in breast cancer women and the control group revealed that the levels of ferroportin were significantly lower in breast cancer patients as compared to the control group. This suggests that ferroportin may play a crucial role in the development and progression of breast cancer. The study also showed that the low serum levels of ferroportin were associated with more advanced stages of breast cancer. The low serum levels of ferroportin in breast cancer patients could, therefore, be contributing to the development and progression of the disease. The findings of this study have significant implications for breast cancer diagnosis, treatment, and management. Ferroportin could potentially be used as a diagnostic biomarker for breast cancer, enabling early detection and intervention. Additionally, treatments that target ferroportin could be developed to prevent or slow down the progression of breast cancer.

### REFERENCES

1. Camilleri E, Gauci F, Bianco SF, et al. Axillary Management of Breast Cancer Patients following identification of Positive Sentinel Nodes at Mater Dei Hospital: An Audit and Literature Review. *Malta Medical Journal*. 2023;35:49-61.
2. Mercieca L, Tonna K, Betts A, et al. Metastatic melanoma mortality in Malta. *Malta Medical Journal*. 2021;33:35-43.
3. Zhelezniakova NM, Tverezovska II. Diagnostic and prognostic value of selenium and Selenoprotein P in patients with comorbid course of nonalcoholic fatty liver disease and arterial hypertension. *Medicinski časopis*. 2022;56:68-76.
4. Ahmed SE, Sarhat ER, Awni N, et al. Altered serum marker of adipokines profile in breast cancer women. *Indian Journal of Forensic Medicine & Toxicology*. 2021;15:2598-2604.
5. Sarhat ER, Abid IM, Kamel NA, et al. Changes of serum Interleukin and Chemerin levels in patients with Polycystic Ovary syndrome. *J Adv Pharm Educ Res*. 2021;11:11- 14.
6. Merkhani MM, Faisal IM, Alsaleem DZ, et al.

Immunodepressant and oxidant potential of standard leukaemia drug regimen. *International Journal of Research in Pharmaceutical Sciences*. 2020;11:1-4.

7. Entedhar R, Sarhat, Madlen Q, Abbas, Nagham H, Ali, et al. Evaluation of ceruloplasmin, sialic acid and liver function for women with breast cancer. *AIP Conference Proceedings*. 2022;2394.
8. Smolarz B, Nowak AZ, Romanowicz H. Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). *Cancers*. 2022;14:2569.
9. Saleh SS, Sarhat ER. Effects of ethanolic *Moringa oleifera* extract on melatonin, liver, and kidney function tests in alloxan-induced diabetic rats. *Indian Journal of Forensic Medicine & Toxicology*. 2019;13:1015-1019.
10. Mahmood DA, Sarhat ER, Sulaiman YA, et al. Evaluation of liver function tests in patients with psoriasis. *Revista Latinoamericana de Hipertension*. 2022;17.
12. Sarhat ER, Zbaar SA, Ahmed SE, et al. Salivary biochemical variables of Liver Function in among Individuals with COVID-19 in Thi-Qar Province. *Egyptian Journal of Chemistry*. 2022;65:305-310.
13. Ghanim H, Mishra S, Sharma D, et al. Studies of biochemical parameters in breast cancer with and without metastasis. *Indian Journal of Clinical Biochemistry*. 2004;19:71-75.
14. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. *New England Journal of Medicine*. 2000;342:564-571.
15. Silcocks PB, Botha JL. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA*. 2012;307:590-597.
16. MacMahon B, Cole P, Lin TM, et al. Age at first birth and breast cancer risk. *Bulletin of the world health organization*. 1970;43:209.
17. Navneet Kaur A. Breast cancer risk factors and second primary malignancies among women with breast cancer. *Breast Cancer Res Treat*. 2015;105:195-207.
18. Almohammadawi KO, Alhilfi HS, Alshewered AS. Epidemiological data of 1418 cancer cases of inpatient in Al-Sadder Teaching Hospital, Misan Province from 2011-2018 (Surveillance study). *Med Sci*. 2018;22:455-461.
19. Abdulsallam A, Thanoon IA, Abduljabbar AI. Propolis-induced hepatorenoprotection in rodents exposed to rifampicin and isoniazid. *MMSL*. 2023;92:75-86.
20. Nwozo SO, Solomon O, Abimbola OO, et al. Comparative study of biochemical and nutritional status of breast cancer patients on chemotherapy/radiotherapy in ibadan. *American Journal of Cancer Science*. 2013;2:51-60.
21. Said NM. Three gold indicators for breast cancer prognosis: a case-control study with ROC analysis for novel ratios related to CBC with (ALP and LDH). *Molecular biology reports*. 2019;46:2013-2027.
22. Alkindi A, Alhashemi W. K. H. Liver Enzyme Parameters in Patients with Breast Cancer: Pre-and Post Radiation therapy. *Eurasian Medical Research Periodical*. 2022;7:112-122
23. Sarhat ER, Siham A, Wadi, Ban I Sedeeq, et al. Study of histopathological and biochemical effect of *Punica granatum* L. extract on streptozotocin-induced diabetes in rabbits. *Iraqi Journal of Veterinary Sciences*. 2019;33:189-194.

24. Sathesh KV, Sharmila S, Premkumar T, et al. Protective effect of umbelliferone against doxorubicin induced cardiotoxicity in Wistar Albino rats. *Sci Technol*. 2016;2:90-98.
25. Damodar G, Smitha T, Gopinath S, et al. An evaluation of hepatotoxicity in breast cancer patients receiving injection doxorubicin. *Ann Med Health Sci Res*. 2014;4:74-79.
26. Anber Z. Effect of doxorubicin and cyclophosphamide regimen versus taxane on liver enzymes in Iraqi women with breast cancer. *Biomedical Research*. 2018;29:3869-3873.
27. Llesuy SF, Arnaiz SL. Hepatotoxicity of mitoxantrone and doxorubicin. *Toxicology*. 1990;63:187-198.
28. Chauhan P, Yadav R, Kaushal V, et al. Evaluation of serum biochemical profile of breast cancer patients. *Int J Med Res Health Sci*. 2016;5:1-7.
29. El-Benhawy SA, Abdelrhman IG, Sadek NA, et al. Studying ferroptosis and iron metabolism pre-and post-radiotherapy treatment in breast cancer patients. *Journal of the Egyptian National Cancer Institute*. 2023;35:1-8.
30. Namgaladze D, Fuhrmann DC, Brüne B. Interplay of Nrf2 and BACH1 in inducing ferroportin expression and enhancing resistance of human macrophages towards ferroptosis. *Cell Death Discov*. 2022;8:327.
31. Geng N, Shi BJ, Li SL, et al. Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells. *Eur Rev Med Pharmacol Sci*. 2018;22:3826-36.
32. Ali ZM, Ali SH, Mohsen FY. Assessment of Some Hematological parameters in Iraqi Women with Different Breast Cancer Stages. *Iraqi Journal of Pharmaceutical Sciences*. 2020;29:99-106.
33. Inoguchi T, Nohara Y, Nojiri C, et al. Association of serum bilirubin levels with risk of cancer development and total death. *Scientific reports*. 2021;11:1-2.
34. Inoguchi T, Fukuhara S, Yamato M, et al. Serum bilirubin level is a strong predictor for disability in activities in daily living (ADL) in Japanese elderly patients with diabetes. *Scientific Reports*. 2019;9:7069.
35. O'Malley SS, Wu R, Mayne ST, et al. Smoking cessation is followed by increases in serum bilirubin, an endogenous antioxidant associated with lower risk of lung cancer and cardiovascular disease. *Nicotine & tobacco research*. 2014;16:1145-1149.
36. Yan M, Wang J, Xuan Q, et al. The relationship between tamoxifen-associated nonalcoholic fatty liver disease and the prognosis of patients with early-stage breast cancer. *Clinical breast cancer*. 2017;17:195-203.
37. Zhu Y, Tian S, Xu L, et al. GELAD chemotherapy with sandwiched radiotherapy for patients with newly diagnosed stage IE/IIIE natural killer/T-cell lymphoma: a prospective multicentre study. *British Journal of Haematology*. 2022;196:939-946.