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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 ВИНИТИ 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 ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

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
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. Корректура авторам не высылается, 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 compu-ter-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.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 საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ 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. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის 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 ფჩხილებში 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.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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INTEGRATED ANALYSIS OF ERA, TP53, AND PGR PROTEINS WITH MIR-372, MIR-373, AND MIR-519D DYSREGULATION IN FEMALE BREAST CANCER

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Abstract.

Background: Breast cancer is the most prevalent cancer among women in the world and is one of the causes of mortality due to cancer. Estrogen receptor alpha (ERα) and progesterone receptor (PGR), as well as tumor suppressor protein TP53, are the hormone receptors that are of critical importance in tumor progression and response to treatment. There is emerging evidence that miRNAs (miR-372, miR-373 and miR-519d) have a role to play in breast cancer pathogenesis by post-transcriptionally regulating genes. Nevertheless, the joint analysis of these protein markers and miRNAs is not studied thoroughly.

Objective: To evaluate serum levels of ERα, TP53, and PGR proteins and assess the expression of miR-372, miR-373, and miR-519d in breast cancer patients compared with healthy controls, and to determine their diagnostic and clinicopathological significance.

Methods: This case–control study included 53 female breast cancer patients and 25 healthy controls. Serum protein concentrations of ERα, TP53, and PGR were measured using sandwich ELISA. Total RNA was extracted from peripheral blood leukocytes, and miRNA expression was quantified using RT-qPCR with the 2^−ΔΔCT method. Statistical analyses were performed using SPSS, including independent t-tests, ANOVA, Pearson correlation, and ROC curve analysis. Statistical significance was set at $p \leq 0.05$.

Results: ERα and TP53 levels in serum were extremely high in patients with breast cancer as compared to controls ($p < 0.001$). There was a significant difference in PGR levels between the stage III and IV disease ($p = 0.01$). Invasion ductal carcinoma (IDC) had significantly higher ERα levels than lobular carcinoma ($p = 0.03$), whereas lobular carcinoma had significantly higher TP53 levels ($p = 0.05$). The miR-372, miR-373 and miR-519d levels of expression were found significantly lower in the patients than in the controls ($p < 0.001$). ROC curve analysis indicated that ERα (AUC = 0.99), TP53 (AUC = 1.0) and PGR (AUC = 0.98) had excellent diagnostic results, whereas miRNAs under study had inverse discriminatory performance. There was strong positive association between ERα, TP53 and PGR ($p = 0.001$) as well as there was strong positive association between the miRNAs being studied ($p = 0.001$). Interestingly, there were significant negative relationships between the level of proteins and the level of miRNA ($p = 0.001$).

Conclusion: High levels of serum ERα, TP53 and PGR have a close correlation with the presence of breast cancer and its subtype variation and have high diagnostic specificity. The down regulation of miR-372, miR-373 and miR-519d may indicate a possible tumor-suppressive effect and regulatory interplay with hormone and tumor suppressor pathways. These results show that protein and miRNA biomarkers are both useful in relation to breast cancer diagnosis, and possibly in determining individual therapeutic approaches.

Key words. Breast cancer, miR-373, miR-519d, Biomarkers, RT-qPCR, ROC analysis.

Introduction.

Breast cancer encompassing various subtypes forms the most current common cancer in females, invoking a consistent effort to identify genetic and epigenetic markers associated with prognosis and therapeutic responses [1]. The regulatory networks underlying breast carcinogenesis are complex, and proteins involved as key players must be thoroughly studied in conjunction with other markers in a context-sensitive manner [2]. The dysregulated expression of the estrogen receptor alpha (ERα), tumor-suppressor protein p53 (TP53), progesterone receptor (PGR), and molecules such as Interleukin-6 (IL=6), Interleukin-8 (IL=8) and miR-372, miR-373 and miR-519d has been analyzed across breast cancer molecular subtypes and specific tumor groups [3].

The roles of ERα, TP53 and PGR, major hormones, cytokines and miRNAs have been investigated, and the possible regulatory axes between them and the corresponding modifications affecting clinical outcome have been considered in a broad perspective [4]. The changes are related to biological processes such as proliferation, differentiation and invasion, and associated with tumor histolabelling, tumor stage and disease-free survival in male breast cancer [5]. A comprehensive and detailed analysis of the interplay between ERα, TP53, PGR and the aforementioned miRNAs, including a mapping of the functional connections and the proposed dysregulation mechanisms, is provided to facilitate the understanding of the contribution to breast tumor progression of mis regulated, interacting players [6].

The ERα signaling pathway is a key driver in ~70% of breast cancers [7]. Through intracellular signaling mechanisms, the product of the ESR1 gene regulates not only the proliferation and differentiation of epithelial cells but also the functions of other proteins, such as TP53 and PGR. TP53 is one of the most studied tumor suppressor genes due to its decisive role in maintaining genomic stability and preventing tumor growth. In ~30% of breast tumors, TP53 function is altered by mutations and misexpression, which changes the hormonal response of breast cancer cells [8]. The function of PGR, the main mediator of progesterone action, normally supports the anti-proliferative effects of oestrogens in hormone-responsive breast tumors. Breast cancers expressing ERα and PR frequently have wild-type TP53 and a diploid genomic status. In contrast, the absence of either ERα or PR is associated with TP53 alterations and aneuploidy, while negative expression of both proteins is often coupled with overexpression of miR-372, miR-373, and miR-519d and with pretumourigenic features [9].

ERα, TP53, and PGR belong to different functional hubs, and the pathways controlled by each of these proteins move away from one another during neoplastic evolution. The evidence indicates that the expression levels of these three proteins are regulated by a concerted action of miR-372, miR-373, and miR-519d. In hormone-responsive tumors, which more directly embody classical ERα-driven biology, the direct action of these miRNAs is counterbalanced by the joint regulatory action of ERα, TP53, and PGR, leading to feedback loops. These principles have implications not only for understanding breast-cancer biology and evolution but also for identifying the main mechanisms responsible for ERα, TP53, PGR, and miR-372, miR-373, and miR-519d misexpression in female breast cancer. The breaking of these regulatory axes may therefore be valuable as a predictive marker of tumour phenotype and progression [10].

Three specific miRNAs, miR-372, miR-373, and miR-519d, are frequently misexpressed in breast cancer. Overexpression studies validate direct repression of TP53 and PGR by miR-372 and miR-373, respectively, while miR-519d promotes miR-372 expression. Notably, these miRNAs adopt an oncogenic role in the tumor context, with burgeoning evidence implicating miR-372 and miR-373 as inducers of epithelial–mesenchymal transition in breast cancer [11,12]. In addition to their individual contributions, the combined action of TP53, miR-372, miR-373, and miR-519d has been shown to trigger a senescence program in breast cancer cells. miR-372 and miR-519d have also recently been identified as modulators of aberrant glycosylation in breast cancer cells [13].

Despite their importance in breast cancer, only a handful of published studies have thus far reported their status or function. The data produced in an extensive body of work support a context-specific role for miR-372 and miR-373, while differential re-expression of mir-372/373/519d signifies the involvement of a broader regulatory circuit, possibly associated with microenvironment changes and tumor progression [14]. The direct regulation of ERα and PGR by a battery of miRNAs has further strengthened the premise that altered expression of hormonal receptors and their strategic regulators hijacks steroid hormone signaling, contributing to the acquisition of aggressive traits by breast tumors. Such observations have prompted the exploration of complementary regulatory relationships, with the current focus centering on miRNA-mediated control of TP53 and downstream pathways in hormone-responsive breast cancer [15]. The interaction among these markers may provide a more cohesive comprehension of tumor biology and facilitate the formulation of personalized treatment plans.

Aim. This study aimed to assess the serum levels of ERα, PGR, and TP53 proteins, as well as gene expression of miR-372, miR-373, and miR-519d in the blood of breast cancer patients in comparison to healthy controls, utilizing ELISA and RT-qPCR, respectively. This investigation aims to identify potential associations and assess the predictive relevance of these indicators in breast cancer progression, diagnostic and treatment response.

Materials and Methods.

Study Design and Sample Collection: This research was executed in the postgraduate laboratory at the Department of Biology, College of Science, and in the Molecular Laboratory of the College of Biotechnology, University of Al-Qadisiyah, Iraq. Peripheral blood samples were obtained from 53 patients (Treated) at the Oncology Center in Al-Karama Teaching Hospital, Al-Zahra Teaching Hospital, and external laboratories located in Wasit province, and 25 healthy individuals were collected as a control group. The stage, grade, and type of breast cancer were determined by clinical pathologists based on standard diagnostic criteria and classifications established by renowned cancer organizations. Each patient provided blood samples, from which serum was separated by centrifugation for subsequent analysis. Ethical approval was obtained before sample collection.

Ethics approval and consent to participate:

The Helsinki Declaration was followed in this study. The University of Wasit Ethics Committee/College of Science Health Directorate approved (Date, July 23, 2025, No. UW.Sci.2025.0723). All study participants gave informed consent.

Inclusion Criteria:

Participants were aged between 18 and 65 years. Patients diagnosed with invasive breast carcinoma, categorized into specific grades (I, II, III), stages (I, II, III, IV), and types (IDC, Lobular, Mixed). Participants may or may not be undergoing chemotherapy, hormonal therapy, or radiation therapy, as the study aims to explore their relationship with marker concentrations. All participants provide informed consent for participation in the study.

Exclusion Criteria:

Participants who are pregnant or breastfeeding. Participants with severe comorbid conditions that might interfere with the study (e.g., autoimmune diseases, severe cardiovascular issues). Patients with conditions unrelated to breast cancer and other cancers.

Enzyme-linked immunosorbent assay (ELISA):

Erα, PGR, and TP53 protein levels in serum samples were measured using a commercial double-antibody sandwich ELISA kit (Elabscience®, China); the category numbers are (E-EL-H6083, EH1449, and E-EL-H0910), respectively. Target antigens are sequentially bound by particular antibodies in this method. The target antigen from the sample is bound by an ELISA plate-immobilized capture antibody. A secondary detection antibody linked to an enzyme (e.g., horseradish peroxidase) binds to the captured antigen-antibody complex. The enzyme subsequently combines with a chromogenic substrate to produce a colorimetric product whose optical density (OD) is proportional to the sample's target antigen concentration. Erα, PGR, and TP53 levels were quantified by comparing sample OD values to a standard curve produced using known antigen concentrations from the ELISA kit. Assay accuracy and consistency were achieved by following the manufacturer's standards, sample, and reagent preparation directions [16].

RNA Extraction:

Peripheral blood specimens were obtained from all individuals

Table 1. Primers of gene expression experiment.

miRNA	Type	Primer name	5'-3'	ACCN	Reference
hsa-miRNA-372	Target	F	TGCTGCGACATTTGAGC	MIMAT0000724	Origene
		R	GAACATGTCTGCGTATCTC		
hsa-miRNA 373	Target	F	AAATGGGGGCGCTTTCC	MIMAT0000725	Origene
		R	GAACATGTCTGCGTATCTC		
hsa-miRNA 519d	Target	F	AGTGCCTCCCTTTAGAG	MIMAT0002853	Origene
		R	GAACATGTCTGCGTATCTC		
hsa-miRNA-16	HKG	F	AGCAGCACGTAAATATTGG	MIMAT0000069	Origene

***HKG:** housekeeping gene.*

Table 2. Comparison of Biomarker Concentrations and Gene Expression Levels between Breast Cancer Patients and Healthy Controls.

ELISA	Groups	Concentration (Mean±S.D.)	P value
ERα	**Control**	244.67±74.23	<0.001***
	BC Patients	1417.77±281.71	
TP53	**Control**	294.81±64.91	<0.001***
	BC Patients	2296.85±446.80	
PGR	**Control**	3.22±0.87	<0.001***
	BC Patients	8.35±3.08	
Gene expression	**Groups**	**Fold Expression**	**P value**
miR-372	**Control**	747.67±237.48	<0.001***
	BC Patients	422.69±334.24	
miR-373	**Control**	80.75±25.65	<0.001***
	BC Patients	45.65±36.10	
miR-519d	**Control**	933.57±280.61	<0.001***
	BC Patients	517.29±409.05	

using standard venipuncture techniques. Whole blood was processed immediately after collection. White blood cells were isolated by centrifugation at 3000 rpm for 10 minutes after red blood cells were destroyed. Total RNA, including miRNA, was extracted from the white blood cells using the HiPure Universal miRNA Kit (Magen, China), following the manufacturer's protocol. The homogenized white blood cells were lysed with MagZol Reagent, and phase separation was performed by adding chloroform. The upper aqueous phase, containing RNA, was purified using HiPure RNA Mini Columns, followed by washing with Buffer RWC and Buffer RW2, and finally eluted with RNase-Free Water. The extracted microRNA was stored at –20°C until use in gene expression analysis and cDNA synthesis.

Primer Design:

Primers for the quantification of target miRNAs (miR-372, miR-373, and miR-519d) and the housekeeping gene (miR-16) were synthesized by Macrogen, Korea, based on mature miRNA sequences from miRBase as shown in Table 1. All reverse primers shared a common sequence (5′-GAACATGTCTGCGTATCTC-3′), while the forward primers were miRNA-specific.

qPCR Gene Expression Analysis (Two-Step Method):

Gene expression analysis was carried out using the GoTaq® RT-qPCR System (Promega, USA) following a two-step reverse transcription and PCR amplification procedure.

In the first step, complementary DNA (cDNA) was synthesized from total RNA (2 µg) using a miRNA-specific reverse transcription approach. For accurate detection of mature miRNAs, a poly(A) tailing strategy was employed prior to cDNA synthesis. Briefly, total RNA was subjected to polyadenylation followed by reverse transcription using oligo(dT)-adapter primers provided in the kit.

The reverse transcription reaction was performed using the AddScript cDNA Synthesis Kit (Addbio, Korea) according to the modified protocol for small RNA detection. The reaction mixture (20 µL) contained 10 µL of 2× Reaction Buffer, 2 µL of 10 mM dNTP Mix, 2 µL of oligo(dT)-adapter primer, 1 µL of Script enzyme solution, and RNA template. The reaction conditions were as follows: 25°C for 10 min, 50°C for 60 min, and 80°C for 5 min.

In the second step, the GoTaq® RT-qPCR System (Promega, USA) was used for the amplification of the cDNA. The PCR reaction mixture was prepared by combining 5 µL of qPCR Master Mix, 0.5 µL of Forward primer, 0.5 µL of Reverse primer, 0.25 µL of $MgCl_2$, 0.25 µL of RT mix, 2.5 µL of Nuclease-Free Water, and 1 µL of cDNA template, bringing the final reaction volume to 10 µL. For each reaction, 1 µL of the cDNA template was mixed with 9 µL of the master mix and added to a PCR tube.

The qPCR amplification was executed by using the adherence to the cycling protocol: initial denaturation for 5 minutes at 95°C, denaturation for 20 seconds at 95°C by 40 cycles of amplification with annealing for 20 seconds at 60° - 65°C for all microRNA, and Extension for 20 seconds at 72°C. A Melting curve analysis was performed at the end of the amplification process, consisting of three cycles from 72°C to 95°C, to confirm the specificity of the amplicons.

Gene expression was quantified using the Livak (2^−ΔΔCT) method. ΔCT values were calculated by subtracting the CT of the housekeeping gene from the CT of the target gene. ΔΔCT was then obtained by comparing ΔCT values between experimental and control groups. The relative fold change in expression was determined as 2^−ΔΔCT.

Statistical analysis:

Analysis of data was done in SPSS. The group differences were evaluated using independent t-test, ANOVA (Duncan test). Pearson test was used to evaluate correlations, Receiver Operating Characteristic (ROC) analysis was done to obtain cutoff values and diagnostic performance. Graphpad Prism was used to prepare the graphs. There are results presented in mean ± SD with the significance level of p 0.05.

Results.

The mean levels of serum concentration of ERα, TP53, and

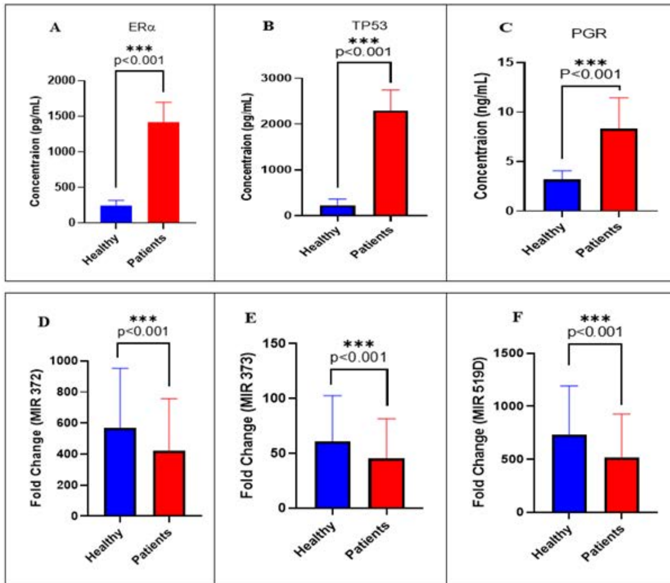

Figure 1. *Differential Expression of Biomarkers and miRNAs in Breast Cancer Patients Compared to Healthy Controls.*

Table 3. *Comparison of Biomarker Concentrations and Gene Expression Levels between Breast Cancer Patients and Healthy Controls across cancer grades.*

ELISA	Grade Groups	Concentration (Mean±S.D.)	P value
ERα	**I**	1439.09±157.96	0.08 NS
	II	1474.45±299.95	
	III	1303.67±247.6	
TP53	**I**	2274.55±142.14	0.76 NS
	II	2267.72±356.43	
	III	2358.88±635.7	
PGR	**I**	8.99±2.42	0.85 NS
	II	8.34±3.12	
	III	8.17±3.28	
Gene expression	**Grade Groups**	**Fold Expression**	**P value**
miR-372	**I**	406.74±331.96	0.87 NS
	II	440.70±346.49	
	III	393.25±325.58	
miR-373	**I**	43.93±35.85	0.9 NS
	II	47.59±37.42	
	III	42.47±35.16	
miR-519d	**I**	497.77±406.25	0.8 NS
	II	539.33±424.04	
	III	481.26±398.44	

PGR proteins and gene expression of miR-372, miR-373, and miR-519d in breast cancer patients and control groups are presented in Table 2. The study revealed a noteworthy increase in the mean concentration ± standard deviation (S.D.) (pg/mL) of ERα and TP53 in patients (1417.77±281.71 & 2296.85±446.80, respectively) compared to the control (244.67±74.23 & 294.81±64.91), with a significant difference at ($P<0.001$) as shown in Figure 1 (A and B). Similarly, PGR (ng/mL) levels were significantly elevated in patients (8.35±3.08) compared to controls (3.22±0.87) at ($P<0.001$) as shown in Figure 1 (C). In qPCR findings, the miR-372, miR-373 and miR-519d gene expression level (fold change) indicated a notable dysregulation

Table 4. *Comparison of Biomarker Concentrations and Gene Expression Levels between Breast Cancer Patients and Healthy Controls across cancer stages.*

ELISA	Stage Groups	Concentration (Mean±S.D.)	P value
ERα	**I**	1456.78±184.52	0.9 NS
	II	1392.93±188.69	
	III	1416.54±264.11	
	IV	1412.63±495.60	
TP53	**I**	2273.46±252.06	0.5 NS
	II	2240.92±345.28	
	III	2262.68±226.30	
	IV	2482.36±911.83	
PGR	**I**	8.05±3.07 ab	0.01*
	II	8.33±3.45 ab	
	III	7.61±2.61 a	
	IV	10.27±2.99 b	
Gene expression	**Stage Groups**	**Fold Expression**	**P value**
miR-372	**I**	490.79±299.32	0.43 NS
	II	349.64±305.19	
	III	480.05±403.24	
	IV	335.16±241.81	
miR-373	**I**	53.0±32.33	0.4 NS
	II	37.76±32.96	
	III	51.84±43.55	
	IV	36.20±26.11	
miR-519d	**I**	600.63±366.31	0.44 NS
	II	427.89±373.49	
	III	587.48±493.48	
	IV	410.17±295.92	

NS: Non-Significant. Different letters indicate a significant difference between the groups. Similar letters indicate non-significant differences.

in the patients group (422.69±334.24, 45.65±36.10 and 517.29±409.05 respectively) as opposed to the control group (747.67±237.48, 80.75±25.65 and 933.57±280.61 respectively) with a significant difference at ($P<0.001$) as showed in Figure 1 (D, E and F).

As shown in Table 3, the analysis of ERα, TP53, and PGR protein concentrations across different tumor grades revealed no significant differences with p value (0.08, 0.76, and 0.85, respectively). Similarly, the gene expression of miR-372, miR-373, and miR-519d across different tumor grades revealed no significant differences with p value (0.87, 0.9, and 0.8, respectively).

As shown in Table 4, the analysis of biomarker concentrations and gene expression levels across different stages of breast cancer revealed some significant findings. For ERα and TP53, no significant differences were observed across stages I to IV, with p-values of 0.9 and 0.5, respectively. However, PGR levels varied significantly, with stage III showing lower concentrations (7.61±2.61) compared to stage IV (10.27 ± 2.99) ($p = 0.01$). Regarding gene expression, miR-372, miR-373, and miR-519d showed no significant differences across stages I to IV, with p-values of 0.43, 0.4, and 0.44, respectively.

As shown in Table 5, the analysis of protein concentrations and gene expression across different breast cancer types revealed several significant findings. For ERα, Invasive Ductal Carcinoma

(IDC) showed a significantly higher concentration (1454.51 ± 258.95) compared to Lobular carcinoma (1154.11 ± 445.26) with a p-value of 0.03, indicating a statistically significant difference between IDC and Lobular types. Regarding TP53, Lobular carcinoma had significantly higher levels (2711.64 ± 1229.56) compared to IDC (2261.66 ± 271.49) and Mixed carcinoma (2172.04 ± 47.93), with a p-value of 0.05. In contrast, PGR concentrations did not show significant differences across the BC types.

Gene expression analysis showed no significant differences for miR-372, miR-373, and miR-519d among the BC types, with p-values of 0.95, 0.94, and 0.9, respectively.

Using ROC analysis, the diagnostic performance of ERα, TP53, PGR, miR-372, miR-373, and miR-519d was evaluated in breast cancer patients and healthy controls, as shown in Table 6 and Figure 2. ERα, TP53, and PGR showed excellent discrimination, with AUC values of 0.99, 0.99, and 0.98, respectively, and cut-off values of 761.98, 962.73, and 4.41, all with highly significant p values (<0.001).

Table 5. *Comparison of Biomarker Concentrations and Gene Expression Levels between Breast Cancer Patients and Healthy Controls across breast cancer type.*

ELISA	**BC Type**	**Concentration (Mean±S.D.)**	**P value**
ERα	**IDC**	1454.51±258.95 b	0.03*
	Lobular	1154.11±445.26 a	
	Mixed	1344.73±39 ab	
TP53	**IDC**	2261.66±271.49 a	0.05*
	Lobular	2711.64±1229.56 b	
	Mixed	2172.04±47.93 a	
PGR	**IDC**	8.22±3.04	0.3 NS
	Lobular	10.05±3.79	
	Mixed	7.66±2.44	
Gene expression	**BC Type**	Fold Expression	P value
miR-372	**IDC**	423.99±326.48	0.95 NS
	Lobular	446.41±441.77	
	Mixed	380.48±356.23	
miR-373	**IDC**	45.79±35.26	0.94 NS
	Lobular	48.21±47.71	
	Mixed	41.09±38.47	
miR-519d	**IDC**	518.87±399.54	0.9 NS
	Lobular	546.31±540.63	
	Mixed	465.63±435.95	

NS: Non-Significant. Different letters indicate a significant difference between the groups. Similar letters indicate non-significant differences.

For miR-372, miR-373, and miR-519d, the AUC values were 0.22, 0.20, and 0.21, respectively. Since these miRNAs were significantly downregulated in breast cancer patients, AUC values below 0.5 indicate inverse discrimination rather than absence of diagnostic value. Lower expression levels were associated with breast cancer, corresponding approximately to reversed AUC values of 0.78, 0.80, and 0.79. Thus, these miRNAs may still have diagnostic relevance as inverse predictors, although their performance requires validation in larger cohorts.

The correlation analysis presented in Table 7 revealed several significant associations between protein markers and miRNAs in breast cancer. ERα showed a strong positive correlation with TP53 (0.81, p = 0.001) and a moderate positive correlation with PGR (0.59, p = 0.001). Similarly, TP53 and PGR were moderately correlated (0.60, p = 0.001). Among the miRNAs, miR-372 was perfectly correlated with miR-373 (1.0, p = 0.001) and strongly correlated with miR-519d (0.9, p = 0.001). miR-373 and miR-519d also showed a strong positive correlation (0.9, p = 0.001). Negative correlations were observed between the miRNAs and the protein markers: miR-372, miR-373, and miR-519d all negatively correlated with ERα, TP53, and PGR, with correlations ranging from -0.36 to -0.4 (p = 0.001), indicating that higher expression of these miRNAs is associated with lower levels of the protein markers.

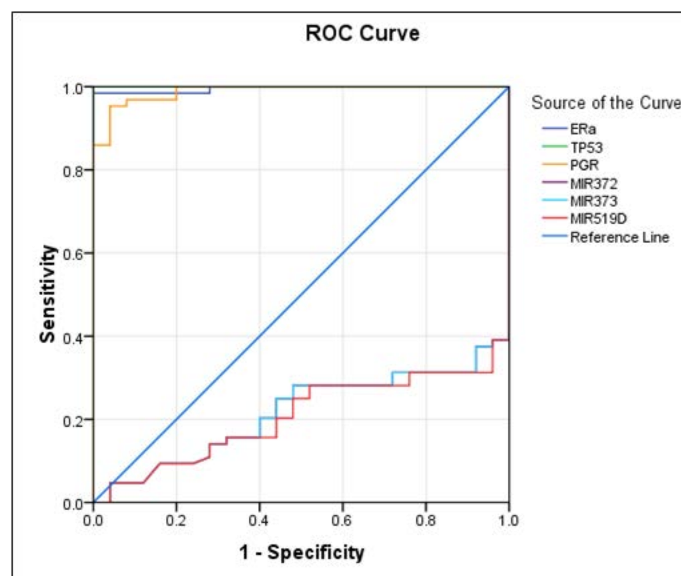

Figure 2. *The ROC Curve for study parameter levels in patients and control groups shows cut-off value, sensitivity, specificity, and area under the curve (AUC).*

Table 6. *ROC curve results for all studied parameters in breast cancer compared with controls.*

ELISA	**AUC**	**Cut-off**	**Sensitivity**	**Specificity**	**Asymptotic 95% Confidence**		**P Value**
					Lower Bound	**Upper Bound**	
ERα	0.99	761.98	98%	100%	0.98	1.005	<0.001***
TP53	0.99	962.73	100%	100%	1	1	<0.001***
PGR	0.98	4.41	95%	96%	0.973	1.004	<0.001***
Gene Expression	**AUC**	**Cut-off**	**Sensitivity**	**Specificity**	**Asymptotic 95% Confidence**		**P Value**
					Lower Bound	**Upper Bound**	
MIR 372	0.22	1227	47%	96%	0.123	0.31	-
MIR 373	0.2	132.6	45%	96%	0.123	0.307	-
MIR 519D	0.21	1502.58	47%	95%	0.116	0.296	

Table 7. Correlation of studied parameters.

Parameter	Pearson Correlation	P-value
ERα & TP53	0.81**	0.001
ERα & PGR	0.59**	0.001
TP53 & PGR	0.6**	0.001
MIR 372 & MIR 373	1.0**	0.001
MIR 372 & MIR 519D	0.9**	0.001
MIR 373 & MIR 519D	0.9**	0.001
MIR 372 & ERα	-0.362**	0.001
MIR 372 & TP53	-0.387**	0.001
MIR 372 & PGR	-0.376**	0.001
MIR 373 & ERα	-0.36**	0.001
MIR 373 & TP53	-0.4**	0.001
MIR 373 & PGR	-0.376**	0.001
MIR 519D & ERα	-0.362**	0.001
MIR 519D & TP53	-0.387**	0.001
MIR 519D & PGR	-0.376**	0.001

Discussion.

Our results demonstrated significantly elevated serum ERα levels in breast cancer patients compared with healthy controls. This finding is consistent with extensive literature indicating that ERα is overexpressed in approximately 70–80% of breast cancers, particularly in luminal subtypes [17]. Previous studies have shown that ERα overexpression promotes estrogen-dependent proliferation and is strongly associated with responsiveness to endocrine therapy. Reports have also confirmed that ERα-positive tumors generally exhibit more indolent biological behaviour and better therapeutic outcomes compared with ER-negative tumors [18].

The significantly higher ERα levels observed in invasive ductal carcinoma (IDC) compared with lobular carcinoma align with prior molecular profiling studies demonstrating subtype-specific ER expression patterns. IDC frequently shows stronger ERα-driven signaling compared with invasive lobular carcinoma (ILC), which may partially explain differences in therapeutic sensitivity and biological behaviour. Therefore, our findings reinforce existing evidence that ERα remains a central driver of hormone-responsive breast cancer and supports its continued value as both a prognostic and predictive biomarker [19].

TP53 Elevation and Subtype Differences.

A significant aspect when the current study is being considered is the identification of ER, PGR, and TP53 in the serum although their localization is clearly intracellular and mainly nuclear. This may be because of a number of biological processes that are associated with the presence of these proteins in the circulation. The active release of intracellular proteins into the bloodstream can be caused by tumor cell turnover, i.e., through apoptosis and necrosis. Moreover, there are nascent findings that tumor-derived exosomes and extracellular vesicles are capable of actively transporting nuclear and cytoplasmic proteins, including hormone receptors and tumor suppressor proteins, to the circulation. Such vesicles are important during intercellular communication and can demonstrate the molecular picture of the tumor-producing cells [20].

Our finding that TP53 levels were significantly higher in lobular carcinoma compared with IDC is noteworthy. While TP53 mutations are traditionally more common in triple-negative and HER2-positive subtypes, recent genomic studies have reported molecular heterogeneity within lobular carcinoma, including cases with complex TP53 alterations [21,22]. These observations support our data and suggest that TP53 dysregulation may contribute to the distinct biological features of lobular tumors [23,24].

Furthermore, it should be noted that the ELISA kits used in this study (Elabscience®, China) are designed to detect total TP53 protein levels and do not differentiate between wild-type and mutated TP53 isoforms. Therefore, the elevated TP53 levels observed in serum likely represent a combined signal of both wild-type and mutant protein forms, particularly given that mutant TP53 is known to exhibit increased stability and accumulation in cancer cells. This limitation should be considered when interpreting the biological and clinical significance of circulating TP53 levels [25].

Our study confirmed significantly increased PGR levels in breast cancer patients compared with controls. This is consistent with earlier reports demonstrating that PGR expression is commonly observed in ER-positive tumors and reflects intact estrogen signaling. Clinically, PGR positivity has been associated with improved response to endocrine therapy and better prognosis [26].

Interestingly, we observed a significant difference in PGR levels between stage III and stage IV disease. Previous literature suggests that PGR expression may decline during tumor progression, particularly in aggressive or hormone-independent tumors. However, some studies have also reported retained or even elevated PGR expression in metastatic ER-positive breast cancer, potentially reflecting adaptive resistance mechanisms to endocrine therapy. Our findings appear to align with this dual behaviour, suggesting that PGR expression may dynamically change during disease evolution and therapeutic pressure [26].

A key contribution of this study is the demonstration of significant downregulation of miR-372, miR-373, and miR-519d in breast cancer patients [27].

Previous research has described miR-372 and miR-373 as context-dependent regulators that may function either as oncogenes or tumor suppressors depending on tumor type and molecular environment. Several breast cancer studies have reported decreased miR-372 expression associated with aggressive characteristics and poor clinical outcomes. Our findings support this tumor-suppressive role in breast cancer [28].

Similarly, miR-373 has been implicated in regulating epithelial–mesenchymal transition (EMT), invasion, and angiogenesis. While some studies describe miR-373 as an oncogenic miRNA in certain malignancies, other breast cancer investigations have documented reduced circulating levels in aggressive disease. The decreased expression observed in our cohort is consistent with reports suggesting that loss of miR-373 contributes to tumor invasiveness [29,30].

miR-519d, a member of the chromosome 19 miRNA cluster (C19MC), has been shown to suppress tumor proliferation and metastasis by targeting oncogenic pathways. Reduced miR-519d expression has been linked to enhanced tumor growth and chemoresistance. Our data align with these observations and

further support its tumor-suppressive function in breast cancer [31].

ROC curve analysis revealed excellent diagnostic accuracy for ERα, TP53, and PGR, with AUC values approaching 1.0 [32]. These findings are consistent with established clinical practice, where hormone receptors and TP53 status are widely used for tumor classification and therapeutic decision-making. Previous biomarker studies similarly report high diagnostic performance for hormone receptor proteins [33].

The miRNA ROC results require cautious interpretation. Because miR-372, miR-373, and miR-519d were downregulated in breast cancer patients, AUC values below 0.5 indicate inverse discrimination, meaning lower expression is associated with disease. However, these findings remain preliminary because ROC analysis was performed in the same cohort without external validation and requires confirmation in larger independent studies [34-36].

Regulatory Interactions and Correlation Analysis.

One of the most significant findings of this study is the strong positive correlation among ERα, TP53, and PGR proteins, along with strong intercorrelation among the three miRNAs and negative correlations between protein levels and miRNA expression [37].

Previous mechanistic studies have shown complex crosstalk between ERα and TP53 pathways, including interactions through AMPK–mTOR signaling. Additionally, ERα and PGR co-expression is well documented in hormone-responsive tumors, reflecting coordinated regulation of steroid signaling [38].

The observed negative correlation between miRNAs and protein markers supports prior experimental evidence suggesting that miR-372, miR-373, and miR-519d can directly or indirectly regulate TP53 and PGR pathways [39,40]. These findings are consistent with earlier reports demonstrating miRNA-mediated modulation of tumor suppressor and hormone receptor signaling [41]. The integrated protein–miRNA axis observed in our study provides further evidence of a feedback regulatory network that may influence tumor progression and endocrine responsiveness [42].

Study Strengths and Implications.

Our study is unique, unlike other past studies that analysed either hormonal receptors or miRNAs individually, we integrated both protein and post-transcriptional regulation layers in the same cohort. The combination of these two methods enhances the concept of breast cancer molecular heterogeneity and multi-marker panels to improve the accuracy of diagnosis [43]. The mechanistic interaction between these miRNAs and hormone receptor pathways requires future functional studies to help clarify it. Also, longitudinal research would be able to reveal the predictive value of these markers to response to treatment or recurrence [44].

Limitations.

Although the diagnostic performance is promising in visualization of this study, it is necessary to take into account a number of limitations. It is important to note that the values of AUC of TP53 and ERa are very high (or almost equal to 1.0), which is not typical in clinical biomarker research and could indicate the possibility of overestimating diagnostic accuracy. This can be explained by the rather limited sample size and using one cohort that lacked external validation.

Also, cut-off values using the ROC were also calculated and tested on the same data, which can create overfitting and restrict the extrapolation of the results. The use of cross-validation or external validation technique would be recommended in future to ascertain the strength and reproducibility of these biomarkers as the good results of these biomarkers have been associated with large and independent cohort.

Conclusion.

The present study offers important information on the molecular landscape of breast cancer, as it analyses the concentration of ERα, TP53, PGR protein levels, and miRNA (miR-372, miR-373, and miR-519d) expression. High concentrations of ERα, TP53, and PGR were detected to be highly related to breast cancer and its responsiveness to treatment and there were high correlations among these proteins. ERα level increase in IDC could also be the explanation of the molecular differences between IDC and Lobular carcinoma. In a similar way, lobular carcinoma exhibited higher TP53 concentration compared to the IDC and Mixed Carcinoma; thus, it is possible that it has specific molecular features that make it behave in a unique way. In stage III, lowering of PGR indicates the development of the tumor to a hormone-independent, aggressive growth and rising of IV stage indicates that tumor is still able to express PGR once it becomes resistant to other endocrine drugs. The research also indicated that there was a dysregulation of miRNA expression and miR-372, miR-373, and miR-519d implying that these miRNAs could act as tumor suppressors in breast cancer. Correlation was done between miRNAs and the protein, and it showed negative correlations with the protein markers, which indicates the complexity of tumor progression regulation and the potential of these miRNAs as a therapeutic choice. They show that although ERα, TP53 and PGR are strong diagnostic biomarkers according to ROC analysis, miRNA-based therapies might present possibilities of enhancement to patient outcomes, specifically in advanced or resistant breast cancer, and help in the diagnostic and prognostic impact of these biomarkers on breast cancer treatment.

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Conflict of interest.

None.

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