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Advancing the Boundaries of Modern Healthcare: Intersections of Biology, Technology, Ethics, and Human Experience

It is with great pride that we present this issue of the journal, which brings together four significant contributions representing some of the most compelling and evolving domains in contemporary health sciences. While varied in focus—ranging from metabolic and vascular biology to artificial intelligence in nursing, the ethics of cosmetic ophthalmology, and the psychosocial implications of breast cancer surgery—their shared relevance lies in their emphasis on the complexity of the human condition. These manuscripts illustrate not only the rapid transformation of medical science and practice, but also the profound interconnectedness between physiology, technology, culture, and personal identity.

The modern era of healthcare requires a multidimensional understanding of disease processes, clinical care, and human behavior. The papers published in this issue reflect this need by challenging outdated paradigms, introducing emerging technologies, and shedding light on underexplored aspects of patient experience, particularly across Middle Eastern and global contexts.

In the systematic review "The Effect of Breast Cancer Surgery on Marital Quality in Saudi Arabia", Khayat sheds light on a profoundly important topic that remains underrepresented in Middle Eastern literature: the impact of breast cancer surgery on marital relationships. Breast cancer carries not only physical and emotional consequences but also deep social and cultural significance, particularly in societies where discussions of intimacy and marital dynamics are often constrained.

Through a synthesis of available empirical studies, the review finds that breast cancer surgery may influence marital quality, body image, self-esteem, sexual functioning, and emotional closeness. Although the existing evidence does not conclusively establish that breast cancer surgery directly undermines marital stability, the review emphasizes clear gaps in regional research—highlighting the need for culturally sensitive, longitudinal, and qualitative studies that address the lived experiences of women and their spouses.

This contribution is especially valuable as it calls attention to the psychosocial dimensions of cancer survivorship in Saudi Arabia. It encourages clinicians to adopt holistic care strategies that include supportive counseling, couple-based interventions, and culturally attuned patient education.

In "Artificial Intelligence in Nursing: A Comprehensive Review", Abyad & Abyad provide an expansive examination of the roles, opportunities, and ethical considerations surrounding the integration of artificial intelligence (AI) in nursing practice, administration, and education. Nursing, comprising the largest proportion of the global healthcare workforce, is uniquely positioned to both benefit from and shape the implementation of AI-driven technologies.

The manuscript explores the diverse applications of AI, including early warning systems for patient deterioration, machine learning models that support clinical decision-making, robotics for safe patient lifting and medication delivery, and natural language processing tools that analyze nursing documentation for safety and quality indicators. These technologies collectively signal a transformation in how nurses assess patients, allocate time, document care, and interact with interdisciplinary teams.

What distinguishes this review is its balanced approach. The authors acknowledge the immense opportunities presented by AI while emphasizing crucial ethical concerns such as algorithmic bias, patient privacy, data governance, and the risk of depersonalizing care. The manuscript calls for a robust AI literacy among nurses and the establishment of ethical governance frameworks to ensure that innovation aligns with human-centered, culturally sensitive, and equitable care.

This article is a timely reminder that AI must not replace the essential human components of nursing, but rather augment them. The future of nursing—particularly in the Middle East, where digital transformation agendas are rapidly expanding—will rely on nurses who are skilled not only clinically, but also technologically, ethically, and analytically

In the manuscript "The Term of Excess Weight Should Be Replaced with Excess Fat Tissue in the Human Body", Helvaci et al. present a persuasive argument for reconceptualizing one of the most widely used yet apparently insufficient constructs

in medicine: "excess weight." Through detailed examination of cardiometabolic patterns, inflammatory processes, and endocrine interactions, the authors propose that excess adipose tissue, rather than excess mass, is the true pathological driver behind systemic atherosclerosis, diabetes, heart failure, chronic kidney disease, and vascular complications.

Drawing comparisons between patients with sickle cell disease—who possess markedly lower BMI yet have extremely low rates of type 2 diabetes—the manuscript advances the theory that adiposity-induced vascular inflammation may be the single most fundamental origin of metabolic disease. This hypothesis aligns with emerging global research that recognizes adipose tissue as an active endocrine organ involved in cytokine release, hormonal disruption, and systemic metabolic instability.

For clinical practice, the implications are substantive. Replacing the simplistic term "overweight" with "excess fat tissue" reframes the clinical conversation by shifting focus from body mass to the inflammatory and metabolic properties of adipose tissue. Such a shift encourages more precise assessment tools, more personalized risk management, and more targeted interventions for chronic inflammatory diseases. Helvaci et al. invite clinicians, researchers, and public health leaders to revisit entrenched terminologies and update them to reflect contemporary understanding of chronic disease biology.

The manuscript "Eye Tattooing, a Facial Extra Pack, and Enhanced Beauty" by Elghblawi explores an area of growing cultural and clinical attention: the use of cosmetic ocular procedures—including scleral tattooing, keratopigmentation (KTP), and laser-induced iris depigmentation—as elective beauty enhancements. Historically used solely for reconstructive or therapeutic purposes, these interventions are increasingly being sought for aesthetic motivations, particularly among younger adults influenced by social media and global beauty trends.

The manuscript presents a comprehensive review of the evolution of these procedures, the associated aesthetic motivations, and, critically, the potential risks. Reported complications include corneal perforation, toxic pigment reactions, severe inflammation, glaucoma, uveitis, and vision-threatening infections. Even more concerning is the fact that many elective procedures are performed outside accredited medical settings, often by practitioners lacking ophthalmologic training.

Elghblawi argues convincingly that regulatory oversight has not kept pace with the rapidly expanding demand for cosmetic ocular interventions. The review highlights the need for stronger clinical governance, public health regulation, and ethical frameworks to ensure patient safety and informed consent. This manuscript serves as a warning that aesthetic innovation must not outpace the standards of safe medical practice.

Synthesis: Toward a Holistic, Ethical, and Forward-Looking Healthcare Paradigm

Although the four manuscripts differ in focus, they share unifying threads that speak to broader transformations in healthcare:

1. A shift toward understanding disease as multidimensional

From adipose-induced inflammation to psychosocial consequences of surgery, disease must be understood in biological, psychological, and social terms.

2. Technology as a defining force in modern healthcare

AI in nursing and aesthetic ocular procedures both highlight the accelerating convergence of medicine and technology—requiring new forms of governance, competence, and ethical reflection.

3. The centrality of ethics

Each manuscript touches on ethical tensions: the language clinicians use, the deployment of AI, the commercialization of beauty procedures, and the cultural framing of marital relationships following illness.

4. Cultural context as a determinant of health experience

Whether examining Saudi marital norms or the popularity of cosmetic eye changes, these papers underscore the importance of cultural sensitivity in healthcare research and practice.

5. The need for interprofessional and interdisciplinary collaboration

Effective solutions in modern healthcare will require clinicians, nurses, researchers, technologists, psychologists, ethicists, and policymakers to work together.

This issue reflects the continuing evolution of healthcare as both a scientific and human endeavor. The manuscripts included herein deepen our understanding of disease mechanisms, highlight the transformative potential of new technologies, illuminate critical ethical considerations, and foreground the lived experiences of patients within cultural and social contexts.

As healthcare systems confront new challenges—from chronic disease epidemics to rapidly advancing digital tools—it is essential that research continue to bridge disciplines and remain firmly anchored in human-centered care. The contributions in this issue move us closer toward a vision of healthcare that is scientifically rigorous, technologically advanced, ethically grounded, and profoundly attuned to the complexities of human life.

THE EFFECT OF BREAST CANCER SURGERY ON MARITAL QUALITY IN SAUDI ARABIA

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Abstract

Background: Breast cancer, accounting for 1 in every 8 cancer diagnoses, is a growing worry for women globally. In Saudi Arabia statistics have shown that BC accounts for over 30% of all recorded cancer cases. Marriage, being the only official relationship between a man and a woman in Saudi Arabia, is put to the test after the diagnosis of breast cancer, hence this systematic review is conducted, to gain knowledge and understanding on the effect of breast cancer surgery on marital quality in Saudi Arabia.

Method: This systematic review with narrative synthesis was conducted following Joanna Briggs Institute's (JBI) integrated mixed method protocol as well as the PRISMA reporting guidelines. The largest biomedical databases were searched in this review: Medline, CINHAL and Psychinfo.
Results: This review is the first of its kind in Saudi Arabia in exploring the influence of treating breast cancer with surgery on marital relationships. Five relevant articles were included (one qualitative and four quantitative). This review synthesised available evidence through narrative synthesis to put data into context and produced four core themes: (1) Women's social role in Saudi Arabia (2) Perceptions of breast cancer (3) Effects on relationship (4) Emotional reactions.

Conclusion: It has not been possible to conclude that breast cancer surgery affects marital quality in Saudi Arabia. However, it has been found that research in SA related to cultural influence on BC and BC effect on marital relationship is lacking greatly and is affecting how women in SA with BC are approached. Therefore, this review will create opportunities for future research in relation to BC effect on marital quality in SA more evidently.

Key words: Breast cancer, Saudi Arabia, Marriage, Breast cancer surgery, marital relationship

Introduction and Background

According to the World Health Organization (WHO), in Saudi Arabia, breast cancer (BC), statistics have shown that BC accounts for over 30% of all recorded cancer cases in the Kingdom of Saudi Arabia (3).

Breast cancer is the abnormal growth and division of cancerous cells in the breasts' ducts and/or lobules (2). Growth might be localized "tumour", or it could spread through blood vessels and lymph nodes to adjacent organs. This spreading process is called metastasis (3). The most common symptoms BC patients present with are changes of the size and/or shape of one or both breasts. Some patients also experience nipple irritation and/or leaking or discharge, as well as pain (4). Although aggressive, the treatment and the management of BC are highly successful with a 90% probability of survival, when detected in the early stages (5). However, due to patients' lack of knowledge and commitment to breast self-diagnosis and performing mammograms regularly, diagnosis is often made in later stages when cancerous cells have grown noticeably (4). First line of treatment of BC is surgery, either total mastectomy or partial removal of the breast known as "lumpectomy", as well as a combination of systematic therapy that is tailored based on the patient's progress and goals (6). Systematic therapy includes anti-cancer medications such as chemotherapy, hormonal therapy, and radiation therapy of affected areas (2,6). On the whole, going through breast cancer's extensive diagnostic and treatment procedures affects women's feminine identity and social role, an effect that lasts even after surviving BC (7).

To move the scene to Saudi Arabia, governments and private organizations are collaborating to increase awareness of BC and encourage women to perform self-diagnosis regularly and provide free mammogram screening for all women above 40 years old (1), yet surveys keep showing insufficient public response to free mammogram and educational classes (8,9,10). This lack of awareness affects women's decision making in relation to their health and wellbeing, making them dependent on resources or people that are not necessarily credible such as their family members, as well as their husbands (11).

When a woman suffers from BC, her whole family is affected by it, and her role as a mother, carer, wife or partner, and daughter changes (7). Therefore, many researchers have shifted their focus on how BC affects not only the patients but their relationships as well, which includes their marriage (11,12,13). Research on different populations has demonstrated that married women's experience with BC is better than single or divorced patients and is associated positively with survival and longevity (13). However, the marital relationship is affected significantly by the diagnosis of BC, causing stress and disruption of marital stability, leading to psychological problems, poor coping, lack of support, and sexual dissatisfaction among patients and their partners (14).

In Saudi Arabia, marriage is a sacred and extremely significant connection as it is the base for forming a family under the religious rules and norms of Islam (15). However, due to the cultural sensitivity related to intimate topics such as the marital relationship, intimacy, and sexual relations, the effect of BC on marital quality is rarely researched, even though it is an important factor in patients' welfare and recovery (12). Marital quality in this review is to be measured by patients' objective description of any changes in their marriage following their diagnosis of BC and treatment with breast surgery.

Aim

This mixed method literature review explores the effect of breast cancer surgery on marital quality in Saudi Arabia. BC surgery is the chosen phenomenon as healthcare professionals opt for breast dissection surgery as the number one treatment of choice in almost all cases (6), and the effect of these surgeries related to Saudi women and their relationship with their husbands is not widely reported in the literature.

The objectives of this systematic review are 1- To increase knowledge on the cultural influence on managing BC and its consequences in SA. 2- Improve BC patients' experience by understanding the effect of their diagnosis and treatment on their families and marital quality in particular. 3- To assess the husbands' role in making health related decisions by their wives in the context of the Saudi culture. Lastly, 4- make recommendations to research and practice to facilitate a smoother and a more holistic approach to BC management.

Method and Design

Review protocol

The main study design the reviewer sought to include in this review was qualitative studies as they allow in-depth exploration of the phenomenon in hand and gain an understanding of an issue from the perspective of participants (16). However, due to the paucity of qualitative studies in the available literature on marital changes related to BC in Saudi Arabia, quantitative studies done on the same topic were also considered in order to get a comprehensive, useful conclusion from combining findings of effectiveness (quantitative) and experience (qualitative) (17), making this review a mixed method systematic review (MMSR) with narrative synthesis.

This integrated MMSR (convergent data based) was conducted following Joanna Briggs Institute's (JBI) framework for evidence-based healthcare (18) and PRISMA reporting guidelines (19). JBI methodology for MMSR was chosen due to its clear and systematic eight steps developed to guide reviewers into conducting a formalized, unbiased systematic review.

Furthermore, following a preliminary database search, the PEO framework was chosen in this review to determine the association between breast cancer surgery and changes in marital quality. This framework is typically used to establish to what degree does the exposure of interest affect an outcome (20). In this review, the P= population is married couples in Saudi, the E= exposure of interest is breast cancer surgery, and the O= outcome is marital quality and stability. Details on the review question format are seen in Table 1.

Table 1: Search question in PEO format:

Q: How does breast cancer surgery affect marital quality of couples in SA?		
Population	Exposure	Outcome
Married couples in SA	Breast cancer surgery	Marital quality

Cochrane library was searched for similar reviews conducted on Saudi married couples, but none were found. A detailed description on how this review was conducted will be specified in the following part, in order to understand the methodology and make this review reproducible by other reviewers.

Search strategy

The largest biomedical databases were searched for relevant studies to answer the review question: Medline (1946 to May 20, 2022), CINHAL (1976 to April 30, 2022) and Psychinfo (1806 to April 30, 2022). No timeframe or limits were set during the search to get as many related articles to the topic as possible. The PEO framework was applied during the database search; however, the outcome (marital quality) was not found as an index term and was substituted by the databases with quality of life; this reduced the specificity of the search and very few related articles were found. As a result, the search strategy was changed to search databases with P and E alone in order to broaden the research and get more related results. This search resulted in more related articles, some of which were qualitative studies, which helped gain a complete understanding of the issue in hand together with the quantitative evidence (21). In addition, reference lists of related articles were scanned as well to find more studies that could answer the review question. Further details on the results are provided in the next chapter.

Medical subject headings (MeSH) terms along with explode option were selected when searching index terms to increase specificity and sensitivity. Truncation (*) was used on some of the keywords to search different endings of the same term at once, the Boolean operator was used to also increase sensitivity; key words are detailed in the facet analysis in Table 2.

Table 2: Facet analysis

Facet analysis	P		E		O *EXCLUDED FROM SEARCH*
Index terms (Mesh)	Saudi Arabia		Breast neoplasms		Quality of life
Key words	Saudi Saudi marri$ Married couples Spouses Husband Wife	A N D	Breast cancer Mastectomy Breast cancer surgery Lumpectomy Reconstructive surgery	A N D	Marital quality Intimacy Marital stability Relationship quality

Studies selected for this review were included based on eligibility by meeting inclusion criteria set by the researcher. Inclusion criteria were English language articles, although all the included studies were conducted in Arabic as it is the native language of the population; they were all translated and published in English. Studies written in languages other than English were excluded due to the cost and time needed for translation. Sample had to be Saudi or people living in Saudi Arabia receiving treatment in Saudi hospitals, diagnosed with breast cancer and treated by surgery as it's the main definer of the population; no age limit was set. Married status, or used to be married during their diagnosis and treatment, was a characteristic for the population. Because marital quality is a focal indicator for this review, any studies done on single women were excluded. Studies that used quality of life indicators or other questionnaires that had marital quality in its measuring elements were also included as they answer the review question indirectly

Data extraction and analysis

Different tools depending on the studies' design were used for critical appraisal. Qualitative studies were appraised using Critical Appraisal Skills Programme (CASP) which had 10 questions (22). For quantitative, cross-sectional studies, Centre for Evidence Based Management (CEBM) tool was used, which consisted of 12 questions that are approved by Oxford centre of evidence medicine (23). Both tools are answered with yes, no or can't tell to help the researcher think systematically; further elaboration of the tool's questions and results are in the findings chapter.

Data was extracted from all eligible articles that met inclusion criteria using Johanna Briggs Institute form for a convergent integrated MMSR (17). The full text of included articles was obtained and carefully revised to ensure all valuable information was methodically gathered and sequentially grouped and coded into meaningful themes via thematic analysis to answer the review question.

A comprehensive narrative synthesis was conducted on the results of included studies to put data into context and find similarities across all studies (24). This process followed three stages established by Popay et al., (2006):

Element.1: A preliminary or initial synthesis was produced by data translation through thematic analysis as seen in the next chapter.

Element.2: Done by discovering commonality of findings, population, and settings of included studies through textual description and tabulation as seen in data extraction while acknowledging the heterogeneity and variability of the included studies' design.

Element.3: Robustness assessment is a process to be applied throughout the analysis and synthesis of a systematic review by using valid tools for critical appraisal, to assess the strength and weight of evidence and support the synthesis process for drawing conclusions or generating hypotheses (24), which was done in this review through quality assessment of included studies that led then to the production of the final core themes.

Findings

This chapter will incorporate search results from all databases and number of included studies that would answer the review question. Then, the quality assessment of the selected studies is discussed. Moreover, detailed results following data extraction of the individual studies included is presented, with a table to summarize these findings. Finally, the chapter presents a comprehensive analysis and synthesis for findings to bring all the data together in a systematic manner.

Search Results

Following the databases search with P= population and E= exposure alone, a total of 1,467 articles came up from the databases searched (Medline= 947, CINHAL= 153, Psychinfo= 367). They were logged and filtered for duplication through a reference manager software Rayyan.ai (25). 573 were duplicates and were removed automatically, and a total of 794 were included for title and abstract screening. Although qualitative studies were the targeted study design to be included in this review, very few qualitative articles were found, and most of those discovered articles could not answer the review question directly as they were conducted on non-Saudi populations. As a result, 785 articles were excluded for irrelevancy and not meeting the inclusion criteria. Only 9 studies remained for the next step of obtaining and reading the full text. Consequently, four studies were eliminated for the following reasons:

1. Wrong outcome measure: Almusa et al. (2019) investigated understanding the depth of knowledge of male partners "husbands" in relation to breast cancer diagnosis and prevention tools, such as self-examination and mammogram and how that affected the number of women getting such education and awareness.

2. Irrelevancy: a grounded theory by Saati et al. (2013), looked into how cultural beliefs affected women's behaviour towards diagnosis and treatment of BC and how the communication between healthcare professionals guided their decision making, without exploring how BC would weigh on their marital relationship.

3. Wrong comparator: Ahmed et al. (2017) a cross-sectional study that assumed that women patients with BC in Saudi Arabia have poor quality of life of and explored their theory by surveying patients. Researchers then linked the results to their clinical qualities of their cancer and their level of physical activity.

4. Wrong population: Sebgul et al. (2021) in an online survey done during COVID-19 times, where their population was husbands only, researchers surveyed husbands to explore their knowledge on BC diagnosis procedures such as breast self-examination and mammogram, however, their wives, as part of the targeted population in this study, were not surveyed or included.

Subsequently, five eligible articles that met the inclusion criteria were included in this review and went through data extraction and quality assessment. A PRISMA flow diagram of the exclusion process is seen in Figure 1.

Quality assessment

Quality assessment conventionally known as critical appraisal is a systematic evaluation that is done to determine the quality of the papers and make an informed decision on whether the clinical evidence in the included articles are reliable, valuable, and useful to answer the review question (26). As this is a mixed methods review it integrated two reliable tools for critical appraisal, Critical Appraisal Skills Programme (CASP) for qualitative studies and Centre for Evidence Based Management (CEMB) for cross-sectional studies.

The only qualitative study included (12) is an interpretive phenomenology that explored women's experience of surviving BC. All the participants had finished treatment which included breast surgery; hence, the study was included to investigate the effect of their condition on their marriage. Of the included cross-sectional studies only one study (27) assessed marital quality directly in relation to breast cancer using The Spousal Perception Scale (SPS) and 89% of their participants were treated with breast surgery therefore, the study was included in the review. The remaining cross-sectional studies (28,29,30) examined the quality of life of BC patients; only indicators that assessed marital satisfaction, directly or indirectly were studied in this review.

Figure 1: Exclusion process in a PRISMA diagram
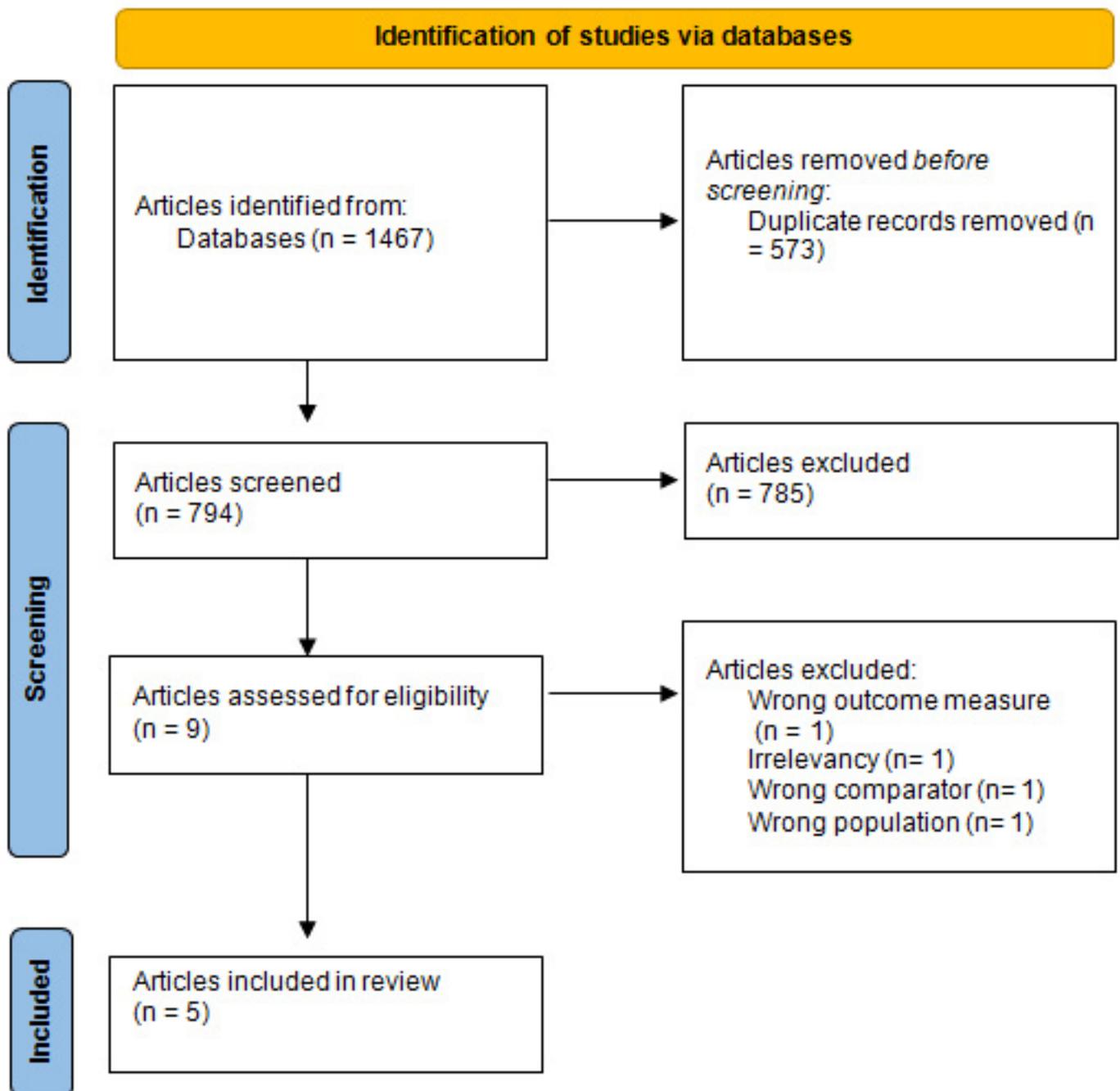
The qualitative paradigm involves exploration and understanding of non-numerical data such as opinions, lived experiences, and underlying reasons from the population's perspective as well as giving meaning to things that are not easily understood (31). The CASP tool for qualitative research was used for quality assessment of the qualitative paper by (12), and is summarized in Table 3, followed by an interpretation of the assessment.

Table 3: Critical appraisal of qualitative study using CASP tool (CASP, 2018):

Items		Answer
1-	Was there a clear statement of the aims of the research?	Y
2-	Is a qualitative methodology appropriate?	Y
3-	Was the research design appropriate to address the aims of the research?	Y
4-	Was the recruitment strategy appropriate to the aims of the research?	C
5-	Was the data collected in a way that addressed the research issue?	Y
6-	Has the relationship between researcher and participants been adequately considered?	C
7-	Have ethical issues been taken into consideration?	Y
8-	Was the data analysis sufficiently rigorous?	Y
9-	Is there a clear statement of findings?	Y
10-	How valuable is the research?	

After completing the quality assessment of the phenomenological study, it was found to be methodical and detailed in its design, synthesis method and results reporting. Questions from 1-5 reveal how useful and clear the aim and results of the study are. Moreover, in such design the risk of potential bias is assessed by presence or absence of certain criteria in the evaluation and appraisal process. These criteria include reflexivity and credibility (32), which were seen as the researcher provided clear links, explanations and justifications of the choices made in each step of the study within the qualitative framework. Question 10 on the value of the research, clarifies and uncovers the struggles and obstacles BC patients face in Saudi Arabia, which is a rare publicly discussed topic in such traditional society, and this adds to the credibility of the research findings as well (26). Another evaluation criterion is transferability, which is lacking as a detailed description of the setting and context in which the interviews were conducted, was not provided.

The remaining studies included in this review were cross-sectional, which is a part of the quantitative design that is non-experimental. In all the included studies in this review descriptive surveys were used that identify and observe the characteristics of a population and the extent of a phenomenon, "breast cancer", by collecting the same type of data at a point of time (33). These descriptive surveys cannot provide robust evidence when generating a hypothesis; however, as they are based on the accuracy of their statistical tests and analysis done on the numerical, objective data gathered, it helps elevate the level of evidence produced (16). The included studies with this design were appraised using the Centre for Evidence Based Management (CEBM) tool summarized in Table 4.

Table 4: Critical appraisal of cross-sectional studies using CEBM tool (CEBM, 2014)

Items / Reference	(Almutairi et al., 2016)	(Nageeti et al., 2019)	(Zahrani et al., 2019)	(Al-Zaben et al., 2015)
1- Did the study address a clearly focused question / issue?	Y	Y	Y	Y
2- Is the research method (study design) appropriate for answering the research question?	Y	Y	Y	Y
3- Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described?	N	Y	Y	Y
4- Could the way the sample was obtained introduce (selection) bias?	N	N	N	N
5- Was the sample of subjects representative with regard to the population to which the findings will be referred?	C	C	C	C
6- Was the sample size based on pre-study considerations of statistical power?	N	N	N	N
7- Was a satisfactory response rate achieved?	C	C		C
8- Are the measurements (questionnaires) likely to be valid and reliable?	Y	Y	Y	Y
9- Was the statistical significance assessed?	Y	Y	Y	Y
10- Are confidence intervals given for the main results?	Y	Y	Y	Y
11- Could there be confounding factors that haven't been accounted for?	Y	Y	Y	Y
12- Can the results be applied to your organization?	N	Y	C	Y

A primary advantage of cross-sectional surveys is the ability to observe a large group of people at once with low costs. However, it is prone to certain biases, including recall bias and response rate bias (33). As all the included studies were done retrospectively, there was a risk of recall bias, and there were no interventions or comments made on how it was counteracted. Moreover, as seen in Table 4, all studies have clearly stated their question, design, and sampling method. In question 5 on representativeness and generalisability, although every study was conducted in a different city in Saudi Arabia, the populations have a lot in common in terms of their religion, cultural practices, and beliefs. However, it is difficult to assume that the findings can be generalized to the whole population as the included studies have not justified the sample size. During the sampling process of the included studies, there were no power calculations mentioned anywhere that would measure the statistical significance of the results and produce the appropriate sample size, which introduces possible selection bias (34). This type of bias may affect the validity of the study as their sample is not representative to the target population (33). Additionally, researchers in included studies have given and received completed questionnaires from participants while being with them in the clinical setting and that increased the response rate and restricted the response rate bias (16).

Data extraction

One qualitative study and four quantitative "cross sectional" studies were included in this review. All studies were conducted in the Kingdom of Saudi Arabia in multiple cities which highlights the similarities and variations of the population regarding cancer in general and BC specifically. The studies were published between 2015-2021. Population was breast cancer patients, regardless of whether they were still receiving treatment or had recovered. Some of the studies were conducted in outpatient clinics while others were conducted with hospitalized patients. Following are the detailed findings of every included study:

In ALmegewly et al.(12) phenomenology paper, they conducted semi-structured, face-to-face interviews with 18 patients; the city in which the patients reside was not mentioned. Written consent was obtained prior to conducting the interviews. Each participant was given around 30 minutes to 2 hours depending on how much they were willing to share. Interviews were conducted in Arabic then translated to English. The population were Saudi female BC survivors, who finished treatment at least 6 months before data collection. No further details on demographic data were collected; sample was selected using purposive sampling. Three themes emerged, 1- meaning of cancer 2- hidden survival and 3- the cultural meaning of survival. Researchers emphasized on the cultural effect on BC survivors in the Saudi population. However, important issues were not discussed with participants such as marital quality changes, body image disturbances, and whether they were supported, or abandoned by their husbands during their journey.

Almutairi et al.(28) cross-sectional paper surveyed 145 female patients diagnosed with BC. They were Saudi nationals, but were seen in multiple outpatient clinics in Riyadh, Saudi Arabia. The population age was over 18 years old, with no history of mental illness; over 50% of them were married and 27% were treated with breast surgery. The study aimed to determine the effect of sociodemographic and clinical characteristics of BC on patients' quality of life using European English for Research and Treatment of Cancer (EORTC) questionnaire, along with a specific questionnaire for BC patients (BR23). Both tools' validity and reliability are known for assessing quality of life (QoL) of cancer patients. The general findings concluded that women with BC in Saudi have lower QoL scores (31.15) compared to other Western (66.5), Asian (65.8), and even other Arabic gulf countries (63.9). Marital status had a significantly positive effect on patients' financial problems, while reduced scores were found in sexual enjoyment. Moreover, patients had positive score in emotional functioning and getting proper emotional support but struggled with physical functioning and how treatment modalities affected them negatively in terms of physical symptoms.

Another cross-sectional study by Nageeti et al.(29) used the same European Organization for Research and Treatment of Cancer (EORTC) questionnaire, to expound the QoL of BC women treated in Saudi Arabia. Researchers surveyed 88 BC survivors in a hospital in Makkah, using convenient sampling. Their population was female patients treated for BC, aged 18 years old or older, who have received any form of cancer treatment modalities. Around 70% of the sample were married women, and 60% were treated with surgery, 79% did not have any reconstructive or plastic surgery after treatment. The general QoL score in that region was (64.0), which varies greatly from the study done in a different city (Riyadh).

Zaahrani et al. (30) cross-sectional study surveyed 96 patients, using non-probability, purposive sampling to recruit Saudi female BC patients from a military hospital in Tabuk. The study aimed to determine the quality of life of women with BC using the quality-of-life instrument for BC patients (QOL-BC) that evaluates the well-being on four aspects of life: physical, psychological, social, and spiritual. Social well-being had elements like family distress, personal relationships, and sexuality, which relates directly to this review's question. 35% of the sample were married and they showed significant higher scores (p > 0.05) than widowed and divorced patients in both physical and social function.

Last included quantitative, cross-sectional study Alzaben et al.(27) was done in a university clinic in the Western region of Saudi Arabia, Jeddah. Using convenience sampling, they surveyed 49 married women with BC, regardless of their nationalities. Participants were given 3 questionnaires, the first one on their demographic data, second on their anxiety scale and the third on quality of marital relations; all tools are valid and reliable in both English and Arabic versions. Researchers aimed to find a relationship between anxiety levels and marital quality. Results have found that 90% of the sample were treated with surgery, and over half of them were Saudi citizens. On marital relations scale, women showed low to moderate scores in terms of spousal support. They averaged 47.6 (SD=8.7) with a theoretical score ranging from 12-66, and finally on the anxiety scale, only 25% had serious anxiety symptoms which was mainly related to their age and education level. No significant relationship was found between marital quality and anxiety levels, but their sample size might be a limitation to these findings.

A summary of the key features and results is seen in Table 5 respectively.

Table 5: Data extraction summary

Reference	(ALmegewly et al., 2019)	(Almutairi et al., 2016)	(Nageeti et al., 2019)	(Zahrani et al., 2019)	(Al-Zaben et al., 2015)
Study design	Interpretive phenomenology.	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Sample size	18 Breast cancer survivors.	145	88 Breast cancer survivors.	96	49
Patient characteristic	Saudi, aged 30-50 y/o.	Saudi, BC patients, >18 y/o.	Females, resided in SA, >18 y/o.	Saudi, females, diagnosed with BC, >18 y/o.	Married women with BC, 18-65 y/o.
Aim	To explore the experience of being a breast cancer survivor in Saudi Arabia.	To assess the quality of life of Saudi female breast cancer patients and determine the effects of the sociodemographic and clinical characteristics on their quality of life.	To assess the quality of life of females with breast cancer in Saudi Arabia and its association with their demographic, social, and clinical data.	To determine the quality of life of women with breast cancer in Tabuk, SA.	To examine the relationship between the quality of marital relationship and anxiety among women with breast cancer in Saudi Arabia.
Setting	Oncology outpatient clinic.	Outpatient units form different clinics, Riyadh, Saudi Arabia	King Abdullah Medical City, Makkah, Saudi Arabia	Surgery Department of King Salman Armed Forces Hospital.	Breast cancer centre at a university hospital.
Outcomes and findings	Three themes emerged. For women in Saudi, breast cancer has a cultural stigma linked to death. It changes the sense of self and of society, leading some women to hide their diagnosis from the public and their families. The meaning of survival in a Muslim context has a cultural and religious base, linked to God's will.	Global health score of participants had a mean score of 31.15 (95% CI 27.79-34.51) (P < 0.005). Poor functioning was found in sexual enjoyment (mean 22.52 [95% CI 17.97-27.08]) while future perspective scored the highest (mean 76.32 [95% CI 70.5-82.12]).	Role functioning scored the highest (mean 71.2, SD = 31), whereas social functioning and emotional functioning scored the lowest, (mean 57 SD = 35.8) and (mean 59.5 SD = 32). The mean global QOL of patients with no children was significantly lower than those who had children (60.2 vs. 64.8, P = 0.043).	The highest score in the psychological well-being subscale was observed for loss of control (8.57±1.11). For the social concern subscale, the highest score was observed for home activities (7.46±1.88), followed by sexuality (7.31±1.86).	The spousal perception scale averaged 16.7 (SD=3.9) on a theoretical range of 6-24, indicating low to moderate support, and the Quality of Marriage Index averaged 31.0 (SD=5.7) on a range of 28-37, indicating moderate scores. The average number of anxiety symptoms was 5.6 (SD=3.8), ranging from 0-15.
Source of funding	Governmental.	Not mentioned.	Not specified.	Governmental.	Not mentioned.

Following the methodology of convergent integrated mixed method systematic review, this review opted to apply narrative synthesis and thematic analysis on the data extracted from eligible studies to arrange data into homogenous groups and generate a connection between studies' "themes" (35).

Thematic analysis and narrative synthesis

A theme is a connection of patterns found in the data set that capture something interesting and important in relation to answering the research question through analysis and interpretation of data rather than summarization (35). This process has been chosen in this review due to its flexibility in the type of data it analyses, as thematic analysis bridges the divide between qualitative and quantitative paradigms (36). Subsequently, this review followed an inductive approach for thematic analysis that allowed themes to emerge from data, molded by the reviewers' knowledge and experience (data led analysis) rather than being pre-set based on theory (36). This approach was chosen due to the scarcity of related articles that answer the review question directly, which gives flexibility to the researcher in developing codes and generating themes. Another analytic choice made for thematic analysis is the coding option; as an inductive approach was taken, semantic coding or descriptive seemed befitting; "it captures the explicit meaning of the data and is built around participants' sayings" (37). A clear 6-step framework for writing the thematic analysis developed by Braun & Clarke was followed in this review. The steps are seen in Table 6.

Table 6: (Braun & Clarke, 2006) framework for thematic analysis

Step 1: Become familiar with the data,	*Step 4: Review themes,*
Step 2: Generate initial codes,	*Step 5: Define themes,*
Step 3: Search for themes,	*Step 6: Produce a report.*

The first two steps of the framework were carried out interchangeably. The reviewer went through the data mass from the selected articles, making associations and connections through reading and re-reading, making observations of repeated ideas and statements across studies, and then grouping these ideas into broad segments "codes" to prepare them and create a rigorous foundation for theme production.

Step 3 was guided by the reviewer's background, answering the review question, and in the analysis of codes. Six raw themes were constructed primarily; a detailed process of this step is seen in the thematic map in Figure 2.

Following that, in steps 4 & 5 of reviewing and finalizing themes, two themes, the effect on marriage and intimate relationship, were combined into one major theme, named effect on the relationship. Moreover, the last theme: impact on husbands, was eliminated as it seemed to lack support from available evidence, even though the theme is of great importance, as marital quality is supposed to be assessed from both parties; husbands and wives . Successively, four final themes were generated: (1) Women's social role in Saudi Arabia, (2) Perception of breast cancer, (3) Effect on the relationship, and (4) Emotional reaction. The articles from which themes were generated from are summarized in Table 7. The final themes were then discussed with the editor in an attempt to eliminate researcher bias in theme selection.

Table 7: Articles in which the themes came from

Articles / Themes	Women's social role in Saudi Arabia	Perception of breast cancer	Effect on relationship	Emotional reaction
(ALmegewly et al., 2019)	X	X	X	X
(Almutairi et al., 2016)	X		X	X
(Nageeti et al., 2019)	X	X		X
(Zahrani et al., 2019)	X	X	X	X
(Al-Zaben et al., 2015)		X	X	X

Figure 2: Primary thematic map
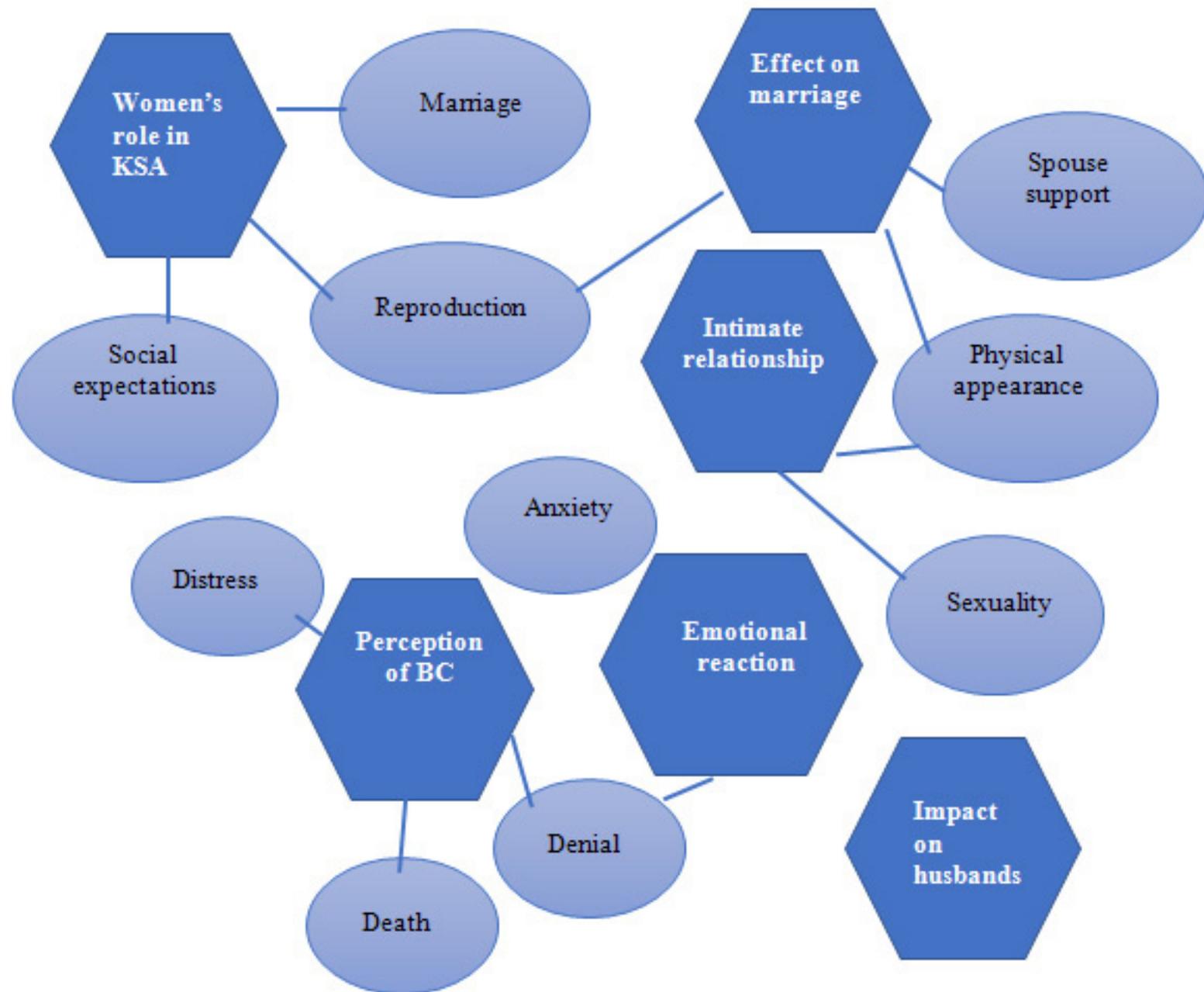
Theme 1: Women's social role in Saudi Arabia.

The first theme focuses on how women's social role is shaped by the culture of Saudi Arabia (SA) and how it affects their marriage. Women in SA are expected to marry and have children at one point in their lives, which in turn is affected or delayed by their diagnosis of BC. It is noted that younger, unmarried patients experienced BC worse than married patients in all aspects of quality of life (12,28). Moreover, as wives, the majority of the house chores and child care falls on the shoulders of women, as men are considered "breadwinners" of the house, and being a BC patient affects that role tremendously. Married women across all the included studies have expressed that their home activity role, which includes their role as wives, was the worst variable to be affected by their BC (mean score= 67.6, 71.2, 74.6) (12,28,30). Furthermore, the culture in Saudi is very inclusive of family members, whether immediate or extended family, and as women carry big responsibilities as mothers and wives, they often hide their diagnosis of BC from their family in order to "protect them" from the worry and fear of BC consequences and to maintain their strong, collective presence for their loved ones instead of being vulnerable and accept the help and support (12).

Theme 2: Perception of breast cancer.

This theme highlights patients' perception of BC in the cultural and religious context of SA which in turn reflects on their decision making on choosing surgery for treatment and the consequences of this decision on their marriage. Across all included studies, women have expressed that BC was a cause of distress in their lives. It interfered with their future plans and dreams, some women even said that upon diagnosis they thought it was the end of their lives (12). Younger patients were shocked when diagnosed with BC and thought of infertility and early menopause (30). While older, uneducated women felt "cursed" for having BC and feared that the illness would transmit to their daughters and sisters (12). In light of religious beliefs, many women accepted their diagnosis as a test from God and were at peace with whatever their fate would be, giving that in Islam people believe that when they endure such suffering, they would be rewarded by God (27). Nevertheless, even though the treatment in Saudi Arabia is free and covered completely by the government, several women expressed fear of the financial burdens following their diagnosis and unemployed women were concerned about the cost of their illness on their husbands and their family as a whole (27,29).

Theme 3: Effect on the relationship.

As marriage is the only legal relationship in SA, this theme was produced to assess the effect of BC diagnosis and treatment on couples' intimacy and the dynamic of their marriage. However, in such a conservative community, the topic of intimacy and private relationship is rarely discussed openly and often talked about in a sensitive and careful manner (27). It is evident as some of the included studies had important scores in sexual enjoyment and sexual relationship, yet no further discussion or comments were made on it (28,30). Furthermore, issues that affect the intimate relationship, like menstrual disturbances and vaginal dryness, were also neglected as women considered this a sensitive and embarrassing topic to discuss with the researchers (29). Additionally, the marital relationship was disturbed by physical changes in body image, like hair loss, weight gain, and mastectomy (27,28,30). As the Islamic religion allows a man to marry more than one woman, BC patients were fearful of losing their husbands and did not have a strong belief that their relationship would withstand this journey. In fact, one woman stated that her husband left her after undergoing BC surgery (12).

Although spousal support and marital quality during BC scored low to moderate when examined, women's expectations of their husband were low, they looked for support when in crisis from their family members and close friends instead of asking their partners (27).

Theme 4: Emotional reaction.

This theme is about patients' emotional reaction to BC as well as the social factors in their lives that affected their emotions either positively or negatively. BC diagnosis was associated with many negative adjectives; patients used words like depression, anxiety, fear, loss of control and death to describe their emotions and experiences (12,28,30). Widowed patients experienced extreme loneliness having to go through the BC journey without a companion or husband on their side. However, support from family members and strong bonds with their close relatives and friends made the suffering more tolerable (12). Additionally, as patients experienced various physical changes, many of them were looked at with pity and were getting lots of negative comments from their surrounding people which made them avoid social gatherings and increased a feeling of isolation (12,27). Young patients have always feared infertility and premature menopause from all the chemotherapy and hormonal therapy they were receiving, that even when recovered patients were interviewed, they were not at ease with their situation and still worried that the cancer might reoccur at any time. Moreover, through all the included studies, patients with lower education and lower socioeconomic status experienced anxiety and stress more severely than educated and employed patients, yet the employed patients worried constantly about losing their jobs from all the sick leave they were on for treatment courses (27,28,29,30).

Discussion

This chapter will critically interpret the findings from this review in the context of other evidence, as well as compare the results with similar reviews done on different populations. Additionally, it will report the importance and implications of this review's findings for both practice and future research. At the end, the challenges and limitations of this review will be discussed.

Results interpretation in context of wider literature

Based on the database research, this is the first review to address the effect of BC on marital quality in Saudi Arabia. This reflects how cultural norms and the community's shyness away from "sensitive" aspects of life related to BC, such as intimacy, breast touching and examination, and opening to strangers about private matters, limits researchers from exploring such a conservative community (11). Moreover, this review question focused on the effect of BC surgery as it is the first line of treatment after diagnosis. Yet, studies that were dedicated to how exposure to BC surgery affected the marital relationship were rather general on the quality of life of affected patients.

It is also worth noting that the majority of included studies (n=4) used questionnaires, which are, although standardized and allow high quality statistical analysis of data, they limit participants' elaboration and explanation on their experiences to only answering the questions predefined by researchers (38).

In this review's findings, the first and third developed themes resonate with another study that was conducted on a culturally compatible population to Saudi; Bahraini women as they are both from the Arabic Gulf region and share the same religion, language, and cultural beliefs. The study aimed to understand the experience of Bahraini women with breast cancer (39). Their results showed how pressured women are by their social role as wives and mothers and how they felt responsible for their families and communities. It was also noted that despite suffering from BC, women feared that their husbands might remarry, given their current condition. They felt obliged to keep their husbands fulfilled by performing their marital duties and preventing any disturbances to the marital dynamic.

In this review, although it is essential to adjust expectations from both husbands' and wives' sides, communication in general was not mentioned nor asked about in all included studies. As a result, patients would suffer and fear in silence without opening up to their husbands and sharing their suffering. In contrast, a literature review on marital adjustment in the context of breast cancer was conducted based on 14 studies from different western countries, mainly the USA and European countries; the reviewers defined marital adjustment as the process in which a married couple achieves a common goal while maintaining individuality (14). Researchers have found that communication was a fundamental influence affecting marital adjustment, and couples who communicated their needs from their partners had a significantly positive effect on their marital adjustment. The western review by (14) has also concluded that the partner's emotional support and involvement during the BC journey affected the marriage positively. This differs from this review's results, which found that Saudi patients sought support from their social circle rather than their husbands.

It was also found in all included studies in this review that younger BC patients experienced worse psychological and emotional distress than older ones as they felt that their lives had been cut short by their diagnosis and that older couples who have been married for a long time and have already had children, felt that their relationship could endure and sustain the distress of BC. The same findings in relation to younger and older patients were also seen in studies on different populations like Bahraini and Chinese (39,40). However, in an older study done in 1999 that looked at the effect of BC on marriage breakdown in Canada, have found that despite the common knowledge that BC causes marital collapse, couples with pre-existing marital difficulties and low marital satisfaction were the ones to struggle after being diagnosed with BC and had higher risks of separating (41).

Furthermore, given the close and involved familial relationship in Saudi, there was a comparable finding from a study done on a Chinese community that asserted the role of family and how extremely important it is that even treatment decisions made by the patient such as getting a mastectomy and undergoing chemotherapy were affected by their family (40).

Whereas in Malaysia, another Asian country that has the same religion as Saudi, they have recognized the familial involvement and understood the husbands' role in decision making. Hence, researchers recommended programs to educate both patients and their husbands to help them in making treatment decisions when diagnosed with BC (42). This intervention would benefit all cultures with great familial involvement, such as SA. Moreover, there was a study that surveyed Saudi male partners to link their knowledge on BC to their wives' utilization of BC screening programs, and it was found that husbands' increased knowledge was significantly associated with their wives' attitude towards breast self-examination and taking mammograms (43).

Although marital relationship and quality are the responsibility of both parties, husbands, and wives, in all included studies in this review researchers have only questioned and interviewed the women alone, leaving the husbands' role vague and unexploited.

Review contribution

Following the database research on marital quality changes regarding BC in SA it was noted that studies are limited and not specific to the phenomenon of interest. This review opens new horizons for further research on the effect of BC on marital relationship in SA and helps understand the phenomenon and assists in formulating policies and guidelines related to management plans of BC.

Overall, future research would benefit from utilizing more complex and meticulous analysis, as well as follow-ups to increase the quality, rigor and trust worthiness of the evidence produced. Like for example, researchers could include husbands when conducting surveys or interviews to get a complete picture of the marital dynamics. Furthermore, conducting more qualitative studies with open-ended questions would create better chances for patients and their families to express and form clearer images of their struggles with BC treatments and its effect on the family as a unit. Researchers could also benefit from assigning female interviewers to help BC women talk more freely about their condition as the culture in SA limits the communication between males and females in regard to intimate subjects.

In practice, apart from exploring the effect of BC on marriage, such reviews on this topic would be a great addition to clinicians, social workers, nurses, and psychologists, in helping them understand the uniqueness of the Saudi culture and ethnicity. It would open doors to ideas like support groups for patients to feel safe and that they are not struggling alone with their fears and difficult issues. Moreover, when a patient's history is being taken, simple inclusion of questions related to marital stability as baseline data will aid in recognizing high risk couples and support them as needed before and during treatment.

Limitations

This systematic review followed JBI steps and guidelines to conduct high-quality review and eliminate bias as much as possible, yet it is not without limitations.

For instance, the synthesis was done by a single researcher in an attempt to answer the review question, although it is recommended that the process be performed by at least two reviewers (24). Nevertheless, specific tools and techniques were used to appraise and synthesize data to ensure transparency, and decisions throughout were discussed with the supervisor to minimize risk of bias and enhance robustness of the evidence.

Conclusion and Recommendation

Succeeding an exhaustive review of the literature following the JBI protocol for integrated mixed method systematic review, it has not been feasible to definitely conclude that BC surgery affects marital quality in Saudi Arabia due to the rarity of published studies. However, it has been found that research related to BC and cultural influence and BC and marital relationship is lacking greatly and is affecting the way women in SA with BC are approached and treated.

Breast cancer remains a global issue that causes dysfunctionality in different aspects of affected women's lives which includes their marriage. Understanding how marital quality changes the outcome of patients being treated for BC, whether in decision making or psychological support, will help healthcare professionals at every level to assess and intervene as needed in order to improve patients' experience, provide the guidance they require, and alleviate their suffering as much as possible.

Recommendation

It is time that sensitive and personal topics like marital relationship in conservative communities be discussed and acknowledged openly as it is the first step to help decision makers understand the struggles of these patients and work on fixing their problems. Thereafter, management of breast cancer should go beyond surgery and physical treatments, as it has been seen through all cultures and religions, that body image changes due to BC surgery and treatments have affected women's self-esteem greatly and created a fear of losing their husbands, which begs the need for psychological referral and evaluation to formulate individualized plans and support all women undergoing BC surgery or chemotherapy. Therefore, future studies should focus on open ended questions that allow researchers to highlight BC women's needs in the context of Saudi Arabian culture.

Ethical consideration

This review does not require ethical approval; however, basic ethical principles were maintained when conducting this systematic review. All included studies have obtained ethical approval prior to conducting their research from designated committees.

There is no conflict of interest within this review.

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THE TERM EXCESS WEIGHT SHOULD BE REPLACED WITH EXCESS FAT TISSUE IN HUMAN BODY

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Abstract

Background: Atherosclerosis may be the main cause of aging and shortened survival.

Methods: All patients with sickle cell diseases (SCD) were included.

Results: We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), stroke (12.1% vs 7.5%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), and clubbing (14.8% vs 6.6%, p<0.001) were all higher in males.

Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan insufficiencies in early decades in SCD. As the most common cause of CRD, diabetes mellitus (DM) may actually be one of the atherosclerotic endpoints of the pancreas. Although atherosclerotic consequences are common in SCD, we have detected no case of DM probably due to lower body mass indexes. So excess fat may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for atherosclerosis. So the term of excess weight should be replaced with the term of excess fat tissue since there are nearly 33 kg of excess fat tissue between the lower border of normal weight and and upper border of overweight in adults.

Key words: Sickle cell diseases, excess weight, excess fat tissue, capillary endothelial inflammation, systemic atherosclerosis, acarbose, metformin

Introduction

Chronic endothelial damage initiating at birth may be the most significant reason of aging and shortened survival via the atherosclerotic consequences in human body (1). Much higher blood pressures (BP) of the arterial system may be the strongest accelerating factor via the repeated injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the destructive process. Therefore venosclerosis is not a significant health problem. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which terminally reduce blood supply to the end-organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical and mental inactivity, emotional stresses, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, abdominal angina, osteoporosis, dementia, early aging, and shortened survival (2, 3). Although early withdrawal of the accelerating factors can delay the consequences, the endothelial changes cannot be reversed, completely due to fibrotic natures. The accelerating factor and atherosclerotic endpoints of the destructive process on vascular endothelium have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (4-6). Similarly, sickle cell diseases (SCD) are highly catastrophic process on vascular endothelium initiating at birth and terminating with an accelerated atherosclerosis-induced multiorgan insufficiencies in much earlier decades (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the chief cause because sickling is rare in peripheral blood samples of patients with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis in human being. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, cancer, and additional stresses. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia in whole body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium especially at the capillary level because the capillary system is the main distributor of the hardened RBC in the body (10, 11). The hardened RBC-induced chronic endothelial damage builds up an accelerated atherosclerosis in much earlier decades. Vascular narrowing and occlusions-induced tissue ischemia and end-organ insufficiencies are the terminal consequences, so the mean life expectancy is decreased 30 years or more in the SCD because we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD in our clinic (8).

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCD were included. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgical procedures, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Patients with a history of one pack-year and one drink-year were accepted as smoker and drinkers, respectively. A full physical examination was performed by the Same Internist, and cases with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and magnetic resonance imagings (MRI) of brain and hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension (14). Hepatic cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, and hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a continuously elevated serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or higher in females. Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of a positive exercise electrocardiogram. Finally, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement

either angiographically or with the Doppler echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke was diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively) into the study, and there was not any patient above the age of 59 years. Associated TM were detected with similar prevalences in both genders (72.5% vs 67.9%, p>0.05, respectively). Both smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), CRD (9.9% vs 6.1%, p<0.05), hepatic cirrhosis (8.1% vs 1.8%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes of the study (Table 2). On the other hand, mean ages of the atherosclerotic consequences were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	p-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	*23.8% (53)*	*<0.001*	*6.1% (13)*
Alcoholism	*4.9% (11)*	*<0.001*	*0.4% (1)*

*Sickle cell diseases   †Nonsignificant (p>0.05)   ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	p-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	*48.1 ± 61.8 (0-434)*	*0.000*	*28.5 ± 35.8 (0-206)*
Disseminated teeth losses (<20 teeth present)	*5.4% (12)*	*<0.001*	*1.4% (3)*
CHD§	*18.0% (40)*	*<0.05*	*13.2% (28)*
Cirrhosis	*8.1% (18)*	*<0.001*	*1.8% (4)*
COPD¶	*25.2% (56)*	*<0.001*	*7.0% (15)*
Ileus	*7.2% (16)*	*<0.001*	*1.4% (3)*
Leg ulcers	*19.8% (44)*	*<0.001*	*7.0% (15)*
Digital clubbing	*14.8% (33)*	*<0.001*	*6.6% (14)*
CRD**	*9.9% (22)*	*<0.05*	*6.1% (13)*
Stroke	*12.1% (27)*	*<0.05*	*7.5% (16)*
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases   †Nonsignificant (p>0.05)   ‡Red blood cells   §Coronary heart disease

¶Chronic obstructive pulmonary disease   **Chronic renal disease   ***Pulmonary hypertension

****Deep venous thrombosis   *****Acute chest syndrome

Table 3: Mean ages of endpoints of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome   †Chronic obstructive pulmonary disease   ‡Pulmonary hypertension   §Coronary heart disease   ¶Deep venous thrombosis   **Chronic renal disease

Disussion

Excess fat tissue may be the most significant cause of vasculitis in human body. DM may actually be one of the atherosclerotic endpoints of the pancreas. Although all of the atherosclerotic endpoints are common in the SCD, we have detected no case of DM, probably due to the significantly lower mean body mass indexes (BMI) of the SCD cases (10). The mean body weights and BMI were 57.8 vs 71.6 kg and 20.7 vs 24.9 kg/m2 in the SCD and control groups, respectively with the mean age of 28.6 years (p= 0.000 for both) (10). Additionally, the heaviest patient was 83 kg in weight in the SCD whereas 111 kg in the control groups (p= 0.000) (10). Interestingly, the body heights were similar in both groups (166.1 vs 168.5 cm, respectively, p>0.05) which may powerfully indicate that the body height is determined, genetically (10). Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for the systemic atherosclerotic process. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes increases parallel to the severity of excess fat tissue (19). The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerotic process may even decrease the clearance of malignant cells by the natural killers (20). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (21, 22). Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) because the fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (23, 24). On the other hand, excess fat tissue will also aggravate myocardial hypertrophy and decrease cardiac compliance further. Fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased parallel to the severity of BMI (25). Similarly, CHD and stroke increased parallel to the severity of BMI (26). Eventually, the risk of death from all causes increased parallel to the severity of excess fat in all age groups, and the cases with underweight may even have lower biological ages and longer survival (27). Similarly, calorie restriction prolongs survival and retards age-related chronic illnesses (28). So the term of excess weight should be replaced with the term of excess fat tissue since there are nearly 19 kg of excess fat tissue even between the lower and upper borders of normal weight and 33 kg between the lower border of normal weight and upper border of overweight in adults.

Smoking may be the second most common cause of vasculitis in human body. It causes a systemic inflammation on vascular endothelium terminating with atherosclerotic end-organ insufficiencies in early decades (29). Its atherosclerotic effect is obvious in the Buerger's disease and COPD (30). Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply, particularly by walking in the feet. It typically begins in extremities but may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also common. Skin ulcerations and gangrene of fingers or toes are the terminal endpoints. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be the main cause of Buerger's disease, particularly in the lower extremities. Multiple narrowing and occlusions in the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may be beneficial in prevention of microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP positive acute phase reactants (APR) in smokers (31). Similarly, smoking was associated with the lower BMI due to the systemic inflammatory effects (32, 33). An increased heart rate was detected just after smoking even at rest (34). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (37). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (38). The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking, so smoking may be more harmful for women probably due to the higher BMI (39). Chemical toxicity of smoking can affect various organ systems. For example, it is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis with several possible mechanisms (40). First of all, smoking may also have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts (41). Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI and GU tracts terminating with IBS and urolithiasis. Finally, immunosuppression secondary to smoking may terminate with the GI and GU tract infections and urolithiasis because some types of bacteria can provoke

urinary supersaturation, and modify the environment to form crystal deposits. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced by the urease producing bacteria. As a result, urolithiasis was higher in the IBS cases (17.9% vs 11.6%, p<0.01) (40).

CHD is the other major cause of death in the human being together with the stroke. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD (43). Probably, excess fat tissue may be the most important cause of CHD because there are nearly 19 kg of excess fat tissue between the lower and upper borders of normal weight, nearly 33 kg between the lower borders of normal weight and obesity, nearly 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2), and nearly 81 kg between the lower borders of normal weight and super obesity (BMI ≥ 45 kg/m2) in adults. In other definition, there is a huge percentage of adults with heavier fat tissue masses than their lean body masses that brings a heavy stress on the heart, liver, kidneys, lungs, brain, and pancreas.

DM is the most common cause of blindness, non-traumatic amputation, and renal dialysis in adults. It may be caused by insulin deficiency, insulin resistance, defective insulins, and/or defective insulin receptors. But excess fat tissue probably takes the major role in its development. Excess fat tissue in liver and pancreas are called as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD). They are usually accepted as components of the metabolic syndrome. NAFLD progresses to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Blocking triglycerides

secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms (44). NAFLD may just be one of the atherosclerotic endpoints, and it is strongly associated with an accelerated atherosclerotic process not only in the liver instead all over the body. For example, NAFLD is seen in one-third of cases with hepatitis B virus-related chronic liver disease (45). Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas (46). The liver density on contrast abdominopelvic CT of colorectal cancer cases was low which is consistent with NAFLD (47). As one of the APR, serum thrombopoietin levels increased in NAFLD (48). Although serum levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in NAFLD (49). As a result, NAFLD is associated with an impaired carotid intima-media thickness (IMT) and flow-mediated dilation which are considered as early markers of systemic atherosclerosis (50). Carotid IMT was correlated with the BMI (p<0.001), age (p= 0.001), and grade 2-3 NAFLD (p<0.001) (51). Patients with NAFLD have more complex CHD, and carotid IMT and grade 2-3 NAFLD were associated with the severity of CHD (p<0.001 for both) (51-53). Similarly, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume in contrast to the increased NAFLD (54). As the most common benign pathologic condition of pancreas in adults, there may be reductions in flow volume of pancreatic arteries in NAFPD, too (55). NAFPD is frequently related with the aging, obesity, and insulin resistance (56). Replacement of more than 25% of pancreas by fat tissue is associated with systemic atherosclerosis and risk of DM (57). Insulin is stored in vacuoles in beta cells of islets of Langerhans all over the pancreas and released via exocytosis. Pancreatic fat infiltration may lead to a reduced insulin secretion (58). NAFPD can lead to exocrine pancreatic insufficiency by fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, destruction of acinar cells by both inflammation and fatty replacement, and by negative paracrine effect of adipocytes (59). It may cause pancreatic fibrosis and cancers. NAFPD causes a higher risk of DM (57), and newly diagnosed patients with DM have significantly greater pancreatic fat content (60). DM may actually be the pancretic fibrosis and insufficiency. Age-related impairment of beta cells may actually be one of the atherosclerotic endpoints since 20% of elderly have DM, and just 55% of patients with DM are obese. Glucose tolerance progressively decreases by aging. It may be due to the progressively decreased physical and mental activity-induced excess fat tissue secreting adipokines. There is no term of malnutrition-related DM. DM can be cured by gastric bypass surgery in 90% of morbid obese cases (61). The effect is not due to the weight loss instead decreased insulin requirement because it usually occurs just after days. This surgery reduced death rate from all causes by 40% (61). NAFPD is an independent risk factor for CHD, too (62). Similarly, the presence of NAFPD is associated with increased aortic IMT and

epicardial adipose tissue (63). According to our opinion, NAFLD, cirrhosis, NAFPD, and DM may just be some of the atherosclerotic endpoints in human body (64).

Acute painful crises are the severest symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stresses are the most common precipitating factors of the crises (65). The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with tissue hypoxia and multiorgan insufficiencies. So the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with multiorgan failures and sudden death with an acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (66, 67). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (66-68). According to our experiences, simple and repeated transfusions are superior to RBC exchange (69, 70). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during such crises (71). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Terminally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints in the SCD. For instance, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (72), and it was associated with the risk of stroke (73). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required (74), but according to our experiences, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden deaths which may develop secondary to multiorgan failures on the atherosclerotic endpoints of the SCD.

Hydroxyurea may be one of the life-saving drugs for the SCD at the moment. It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis (75, 76). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial cells damage-induced edema, ischemia, and infarctions (77). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (78). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (79). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea group that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (79). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (79). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5, annually (79). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7, annually (p<0.000) with an additional decreased severity of them (7.8/10 vs 2.2/10, p<0.000) (66). Parallel to us, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (80). Although the genetic severity remains critical to determine prognosis, hydroxyurea may decrease severity of disease and prolong survival (80).

The complications start to be seen even in infancy. For example, infants with lower hemoglobin values were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (81). If started in early years, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. But due to the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult, RBC transfusions should be kept just for emergencies as the most effective weapon in our hands at the moment.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for the synthesis of prostaglandins (PG) and thromboxanes (TX). PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. But aspirin does not decrease the blood viscosity. The antithrombotic property of aspirin is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke (82). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (83). According to the literature, aspirin may also be effective in prevention of colorectal cancers (84). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin should not be prescribed for febrile patients under the age of 12 years (85). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (86). Reye syndrome is a rapidly worsening brain disease (86). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (87). The syndrome mostly affects children, but it can only affect fewer than one in a million children, annually (87). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (86). Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen (86). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (86). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (87, 88). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (86). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (87). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (89).

Warfarin is an anticoagulant, and it does not have any effect on blood viscosity, too. It can prevent formation of blood clots and reduce the risk of thromboembolism. Warfarin is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent blood clots formation as in DVT and pulmonary embolism, and to protect against stroke in atrial fibrillation (AF), valvular heart disease, and artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in the ambulatory settings (90). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (91). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5 (92). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect, and these effects can last for up to five days. The consensus agrees that current self-testing and management devices are effective methods of monitoring oral anticoagulation therapy, providing outcomes possibly better than achieved, clinically. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is just 1-3%, annually (93). All types of bleeding may occur, but the severest ones are those involving the central nervous system (92). The risk is particularly increased once the INR exceeds 4.5 (93). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (94). Thirteen publications from 11 cohorts including more than 48.500 patients with more than 11.600 warfarin users were included in the meta-analysis in which in patients with AF and non-end-

stage CRD, warfarin resulted in a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) (95). Similarly, warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (96). Whereas recurrent ICH occured in 6.7% of patients who used warfarin and 7.7% of patients who did not use warfarin (p>0.05) (96). On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens (97). Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes (98). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term use of low-dose warfarin is highly effective and safe with a reduction of 86% in the risk of stroke (p= 0.0022) (99). The mortality rate was markedly lower in the warfarin group, too (p= 0.005) (99). The frequencies of bleedings that required hospitalization or transfusion were similar in both groups (p>0.05) (99). Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value was 1.5 (100). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleedings as for warfarin, but increased GI bleeding (101). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (102). The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups, respectively (p>0.05 for both) with AF in another study (103). On the other hand, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths (104). So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving regimen to decrease severity of capillary endothelial inflammation, and to prevent atherosclerotic endpoints even at childhood in the SCD (105). COPD is the third leading cause of death in human being (106, 107). Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the major causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints all over the body. Regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (108). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (109). Probably an accelerated atherosclerotic process is the main structural

background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary endpoint of the systemic atherosclerotic process. Beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (110). For instance, there may be close relationships between COPD, CHD, PAD, and stroke (111). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (112). When hospitalizations were researched, the most common causes were the cardiovascular diseases, again (112). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (113). Finally, COPD may be the pulmonary endpoint of the accelerated atherosclerotic process in the SCD (106).

Leg ulcers are seen in 10% to 20% of the SCD (114). Its prevalence increases with aging, male gender, and SCA (115). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (114). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (114). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (115). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (116). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (117). Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. Similarly, lower WBC counts were associated with lower crisis rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (78). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial cell inflammation and edema.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (118). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (119). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, clubbing is frequently associated with the pulmonary, cardiac, renal and hepatic diseases, and smoking those are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, clubbing is also common in the SCD with a prevalence of 10.8% in the present study, too. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%, p<0.001) may also indicate some additional role of male gender about the atherosclerotic endpoints.

CRD is also increasing that can also be explained by aging of the human being and increased prevalence of excess weight all over the world (120). Aging, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (121). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation (122). For instance, age (p= 0.04), high-sensitivity CRP (p= 0.01), mean arterial BP (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (120). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (123). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (123). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (124). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM, CRD progresses much more easily (123). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (125). Although some authors reported that alcohol was not related with the CRD (125), various metabolites of alcohol circulate in blood vessels of kidneys and give harm to the endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (124). Due to the systemic nature of atherosclerosis, there are close relationships between CRD and other atherosclerotic endpoints of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (126, 127). For example, the most common causes of death were the CHD and stroke in the CRD, again (128). The hardened RBC-induced capillary endothelial damage cell may be the major cause of CRD in the SCD, again (129).

Stroke is the other terminal cause of death, together with the CHD, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious processes, cancers, and emotional stress may be the major underlying causes. Stroke is also a common atherosclerotic endpoint of the SCD (130). Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts (131). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial cell damage, inflammation, edema, and fibrosis (132). Probably, stroke does not have a macrovascular origin in the SCD, and acute onset diffuse capillary endothelial cell damage, inflammation, and edema may be much more significant. Eventually, permanent neurological deficits of stoke are rare in cases with the SCD. Infection, inflammation, medical or surgical emergency, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. Decreased stroke with hydroxyurea can also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced an acute onset accelerated capillary endothelial cell edema in the SCD (133).

Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. Acarbose binds to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Actually, it does not have any direct effect on glucose absorption. It should be taken with the first bite of the meal, and its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use without any treatment failure. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, accounting for the frequency and severity of GI adverse effects such as flatulence, loose stool, and abdominal discomfort (134). If

started with a lower dosage and titrated slowly, it tends to cause tolerable GI side effects (135). Long-term use increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use even in cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease carcinogenesis. After oral administration, less than 2% of the unchanged drug enters into the circulation. Thus there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (136). The initial improvement in blood glucose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years. Its beneficial effects on serum lipids were also seen with a dose-dependent manner (136), because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglycerides synthesis is reduced for several hours, so acarbose lowers plasma triglycerides levels (136). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) (137). Significantly elevated ursocholic acids in the stool appear to be the additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in DM (138). Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction (136). So it prevents all atherosclerotic endpoints of excess fat even in the absence of IGT or DM (139-141). Although some authors reported as opposite (142), it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect or toxicity (143).

Metformin is a biguanide, and it is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption (144, 145). Precise mechanism of intracellular action of metformin

remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite (146). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (146). According to our opinion, the major effect of metformin is a powerful inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported (147-149). Probably the major component of the metabolic syndrome may be excess fat tissue and its atherosclerotic endpoints which can be prevented by suppression of appetite. So treatment of excess fat with metformin will probably prevent not only the IGT or DM but also most of the other atherosclerotic endpoints. Due to the low risk of side effects, metformin can be initiated for majority of cases. Although 25.9% of patients stopped metformin due to an excessive anorexia (146), only 10.6% stopped acarbose due to an excessive flatulence or loose stool (150). So acarbose intolerance is lower than metformin in the society (p<0.001) (146). Eventually, acarbose can be used in a larger population, and we should not put a lower limit of age to start acarbose for cases with excess fat tissue.

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan insufficiencies in early decades in the SCD. As the most common cause of CRD, DM may actually be one of the atherosclerotic endpoints of the pancreas. Although the atherosclerotic consequences are common in SCD, we have detected no case of DM probably due to the significantly lower BMI of them. So excess fat tissue may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for the systemic atherosclerosis. So the term of excess weight should be replaced with the term of excess fat tissue since there are nearly 33 kg of excess fat tissue between the lower border of normal weight and and upper border of overweight in adults.

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ARTIFICIAL INTELLIGENCE IN NURSING: A COMPREHENSIVE REVIEW

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Abstract

Artificial intelligence (AI) represents one of the most consequential technological transformations in modern healthcare, enabling unprecedented capabilities in prediction, automation, simulation, and decision support. Nursing, as the largest segment of the global health workforce, stands at the center of this transformation. AI not only enhances clinical decision-making and early recognition of patient deterioration, but it also impacts nursing education, administrative processes, and research methodologies. This expanded narrative review synthesizes a wide range of empirical evidence and conceptual literature to examine how AI is reshaping the nursing profession. The review discusses machine learning (ML), natural language processing (NLP), robotics, virtual simulation, and decision-support systems in the context of clinical practice, education, management, and research. Ethical, legal, and professional implications are also explored, with emphasis on algorithmic bias, data governance, explainability, and the preservation of the nurse–patient relationship. Two comprehensive tables summarize clinical applications and implementation challenges.

The review concludes with recommendations for practice, governance, and future research, emphasizing the critical importance of AI literacy and human-centered design to ensure equitable, transparent, and compassionate use of AI technologies in nursing.

Keywords: artificial intelligence, nursing, machine learning, decision support, nursing education, ethics, robotics

Introduction

Artificial intelligence (AI) has evolved from simple rule-based programs to sophisticated learning systems capable of synthesizing complex datasets, recognizing patterns, and generating insights traditionally requiring human cognition (Topol, 2019). The adoption of AI in healthcare is accelerating rapidly due to advances in machine learning (ML), natural language processing (NLP), computer vision, robotics, and large language models (LLMs). Specific clinical disciplines—including radiology, oncology, pathology, and cardiology—have already experienced major AI-driven disruption.

Because nurses form the backbone of healthcare delivery, AI's integration into nursing practice has profound implications. According to the World Health Organization (2020), nursing accounts for 59% of the global healthcare workforce, making nurses central to digital transformation. Nurses perform continuous assessment, monitoring, intervention, coordination, patient education, and documentation—activities that intersect directly with AI applications (Joo & Liu, 2021).

AI has demonstrated significant potential to:

- Identify early signs of deterioration
- Predict falls, sepsis, cardiac arrest, and readmission
- Reduce documentation burden
- Personalize patient education
- Support clinical reasoning in nursing students
- Optimize staffing and resource allocation
- Analyse big data for research (Krittanawong et al., 2021; Shickel et al., 2018)

However, concerns regarding equity, transparency, privacy, and the impact on relational aspects of nursing remain critical (Morley et al., 2020; Turale & Nantsupawat, 2021). Thus, understanding AI's impacts requires integrating empirical evidence with ethical and professional frameworks.

This comprehensive, thesis-level manuscript analyses AI applications across four domains:

1. Clinical nursing practice
2. Nursing education and simulation
3. Nursing administration and workforce management
4. Nursing research

It also explores nurses' perceptions, ethical issues, regulatory considerations, and future directions for AI in nursing.

Defining Artificial Intelligence in the Nursing Context

AI in healthcare refers to computational algorithms that mimic human cognition through machine learning, deep learning, NLP, and predictive modelling (Topol, 2019). For nursing specifically, AI can be conceptualized in the following categories:

1 Machine Learning (ML)

ML algorithms learn patterns from data to make predictions. They include supervised, unsupervised, and reinforcement learning models. In nursing, ML is used to:

- Predict sepsis (Henry et al., 2015)
- Detect early deterioration (Taylor et al., 2016)
- Forecast falls (Williams et al., 2021)
- Predict pressure injuries (Oh et al., 2021)
- Identify readmission risk (Mortazavi et al., 2016)

ML interpretations vary from black-box deep learning models to interpretable models like decision trees.

2 Deep Learning

Deep learning (DL) uses multi-layer neural networks capable of analysing high-dimensional data such as imaging, waveforms, or continuous monitoring data. DL has been applied to:

- Wound assessment via image analysis
- Gait pattern recognition
- Arrhythmia detection
- Pulmonary and cardiac imaging classification (Rajpurkar et al., 2017)

3 Natural Language Processing (NLP)

NLP transforms clinical text into analysable data. Nursing documentation—rich in narrative detail—benefits particularly from NLP for:

- Extracting symptoms, interventions, and assessments
- Analysing triage narratives
- Evaluating care plans
- Coding free-text notes (Ford et al., 2016)

4 Robotics

Robotics supports physical and social care tasks, including:

- Lifting and transfer
- Remote telepresence
- Medication delivery
- Companionship for older adults (Bemelmans et al., 2012)

5 Conversational AI and Virtual Nursing Assistants

Conversational agents provide:

- Medication reminders
- Symptom triage
- Preoperative education
- Chronic disease support (Bickmore et al., 2018)

6 Computer Vision and Wearables

Computer vision analyses video to detect falls, bed exits, wound progression, or unsafe behaviour. Wearables provide continuous monitoring of:

- Heart rate
- Activity level
- Oxygen saturation
- Sleep patterns (Stehlik et al., 2019)

7 AI-Enhanced Simulation and Education

AI powers adaptive virtual patient simulations. These systems mimic human responses and improve clinical reasoning, communication, and teamwork (Padilha et al., 2019).

AI in Clinical Nursing Practice

AI has made the greatest impact in clinical nursing, where technologies support assessment, monitoring, intervention, and clinical reasoning across multiple care settings—from acute care to community and long-term care (Table 1).

1 Predictive Analytics and Early Warning Systems (EWS)

Predictive models have emerged as one of the most mature applications of AI in nursing. ML-based early warning systems can detect subtle physiological trends that traditional scoring systems may miss. For instance, ML models for sepsis prediction have demonstrated improved sensitivity compared with the Modified Early Warning Score (MEWS) (Henry et al., 2015; Taylor et al., 2016).

Predictive analytics is the most mature AI application in clinical nursing.

1.1 Predicting Sepsis

Sepsis remains one of the leading causes of hospital mortality. ML-based algorithms detect subtle physiologic changes earlier than conventional vital sign thresholds.

- The TREWScore model predicted septic shock hours earlier than clinicians (Henry et al., 2015).
- ML sepsis models have demonstrated increased sensitivity and specificity compared to traditional scoring systems like MEWS and NEWS (Taylor et al., 2016).

1.2 Predicting Deterioration and Cardiac Arrest

ML models predict deterioration using:

- Vital sign trajectories
- Laboratory trends
- Nursing documentation
- Sensor data (Chen et al., 2020)

Early detection helps nurses prioritize workload and escalate care efficiently.

1.3 Predicting Falls

Falls are one of the most preventable inpatient harms.

ML fall models incorporate:

- Medications
- Gait patterns
- Mobility data
- Night-time restlessness
- Prior fall history (Williams et al., 2021)

1.4 Predicting Pressure Injuries

ML models using EHR data outperform the Braden Scale by integrating dozens of risk features (Oh et al., 2021).

1.5 Predicting Readmissions

ML readmission models identify high-risk patients, enabling targeted discharge planning (Mortazavi et al., 2016).

2 Clinical Decision Support Systems (CDS)

AI-enabled clinical decision support (CDS) delivers recommendations integrated into electronic health records. These systems assist with:

- Alerts for harmful drug interactions
- Wound care recommendations based on wound characteristics
- Fluid management indicators
- Infection control suggestions
- Automated early sepsis alerts (Wong et al., 2021)

Studies demonstrate that AI-CDS systems can reduce medication errors and improve guideline adherence (Ginestra et al., 2019; Wong et al., 2021). However, poorly designed systems may worsen alert fatigue and increase cognitive load for nurses, underscoring the need for human-centered design.

3 AI-Enhanced Monitoring and Smart Environments

AI-embedded monitoring systems support continuous patient assessment. Computer vision and ML tools can detect bed exits, monitor mobility, identify respiratory distress, and track vital-sign trends (García-Magariño et al., 2019).

Table 1. Examples of AI Applications in Clinical Nursing Practice

Domain	Example AI Function	Primary Nursing Benefit	Key Considerations
Deterioration / sepsis	ML-based early warning scores	Earlier detection, timely escalation	Alert fatigue, explainability
Falls prevention	Predictive fall-risk models + vision monitoring	Targeted rounding, bed-exit alerts	Privacy, false positives
Pressure injury prevention	Risk prediction based on nursing assessments	Prioritized repositioning, surface selection	Data quality, workflow integration
Medication safety	AI-enhanced infusion pump checks	Reduced programming errors	Liability, training
Chronic disease management	Wearable-based risk scores (e.g., HF, COPD)	Early outreach, tailored education	Equity of access, connectivity
Patient education	Conversational agents / virtual nurses	24/7 education, standardized information	Trust, cultural sensitivity, oversight
Critical care monitoring	Multimodal predictive models	Workload prioritization in ICU	Interdisciplinary governance

Wearables paired with AI predict exacerbations of chronic illnesses such as COPD and heart failure (Stehlik et al., 2019). These tools offload monitoring burden but raise questions about reliability, data accuracy, and responsibility distribution.

Continuous monitoring is essential to nursing. AI automates interpretation of:

- Bedside monitors
- Wearable devices
- Motion sensors
- Ambient monitors

Applications include:

- Detection of respiratory distress
- Bed exit prediction via computer vision
- Real-time monitoring of post-surgical patients
- Wearable-based detection of heart failure decompensation (Stehlik et al., 2019)

4 Social and Assistive Robotics

Robots such as PARO and NAO have been used in geriatric and dementia care to support emotional well-being, cognitive stimulation, and social engagement (Bemelmans et al., 2012). Telepresence robots allow nurses to interact remotely with patients during infectious disease outbreaks (Papathanasiou et al., 2020).

Robotic integration has produced mixed reactions among nurses: improved efficiency but concerns about depersonalization and skill erosion (Cresswell & Sheikh, 2021).

Robots reduce physical strain and enhance safety.

Types of robots in nursing:

- ***Assistive robots:*** lifting, turning, feeding
- ***Social robots:*** PARO for dementia care (Bemelmans et al., 2012)
- ***Telepresence robots:*** remote consultations
- ***Logistics robots:*** supply transport

Robotics adoption must be carefully managed to maintain human connection.

5 Effects on Patient Outcomes and Nursing Workload

A growing body of evidence suggests that AI can:

- Improve accuracy of clinical decisions (Rajpurkar et al., 2017)
- Reduce documentation time (Shah et al., 2021)
- Decrease adverse events (Taylor et al., 2016)
- Increase time for direct patient care (Cattell et al., 2018)

Nevertheless, benefits depend on workflow integration and local context. Poor implementation can create new burdens rather than alleviate existing ones.

AI in Nursing Education and Simulation

Advances in artificial intelligence have transformed nursing education through innovations in simulation, virtual learning environments, automated assessment, and predictive learning analytics. These technologies help prepare a future workforce equipped to practice in increasingly digital clinical environments.

1 AI-Driven Simulation and Immersive Learning

Simulation has long served as a foundational teaching method in nursing education, offering safe environments for skill development. AI-enhanced simulation significantly elevates traditional approaches by enabling dynamic, adaptive, and highly realistic scenarios.

1.1 Virtual Reality (VR) and Augmented Reality (AR)

AI embedded within VR and AR platforms allows simulation environments to respond fluidly to learner decisions.

- VR simulations improve clinical reasoning, reduce anxiety, and enhance decision-making accuracy (Foronda et al., 2020).
- Meta-analysis demonstrates VR-based education produces equivalent or superior learning outcomes compared to traditional simulation (Kyaw et al., 2019).
- AI-driven clinical avatars can imitate complex patient behaviours, including emotional responses, deteriorating conditions, or subtle clinical cues

1.2 Benefits to Clinical Competency

AI-enhanced simulations support:

- Holistic patient assessment
- Safe repetition of rare or high-risk scenarios
- Team-based dynamic response training
- Immediate formative feedback
- Reduction of faculty workload, as AI can analyse learner performance autonomously

1.3 Expansion in Graduate Nursing Programs

Nurse practitioner programs increasingly incorporate AI simulation to teach advanced assessment, diagnostic reasoning, and pharmacologic decision-making.

2 Virtual Patients and Conversational AI

Virtual patients (VPs) simulate interactive patient encounters. Unlike static case studies, AI-powered VPs adapt to student questions and demonstrate realistic variability.

2.1 Clinical Interviewing and Communication Skills

AI VPs enable students to practice:

- Motivational interviewing
- Mental health assessment
- Pediatric communication
- Breaking bad news
- Cultural competence through variable patient profiles

2.2 NLP-Based Dialogue Engines

NLP enables virtual patients to "understand" student questions and respond appropriately. This enhances realism and prepares students for clinical conversations where patient responses are unpredictable (Padilha et al., 2019).

3 Intelligent Tutoring Systems (ITS)

AI-powered intelligent tutoring systems deliver personalized instruction, identifying knowledge gaps and streamlining learning.

3.1 Adaptive Learning Pathways

ITS systems monitor student performance across:

- Pharmacology
- Pathophysiology
- Clinical judgment
- Documentation
- Safety competencies

Algorithms adjust difficulty, suggest remedial content, and optimize learner progression (Zawacki-Richter et al., 2019).

3.2 Automated Assessment and Feedback

NLP enables automated scoring of students' clinical notes, SOAP notes, and care plans, providing instant feedback.

3.3 Learning Analytics for Student Support

AI can identify students at risk of academic failure weeks before traditional assessments.

4 Challenges in AI-Augmented Education

4.1 Algorithmic Bias and Equity

Biased training data may produce biased assessments of students, reinforcing inequities.

4.2 Threats to Authentic Human Mentorship

AI cannot replicate the empathetic, relational aspects of nurse educator support (Willemse et al., 2019).

4.3 Faculty Preparedness

Many nursing faculty lack training in AI technologies, leading to inconsistent implementation and resistance (Islam et al., 2020).

4.4 Surveillance Concerns

AI-based learning analytics raise issues of student privacy, autonomy, and consent.

5 AI in Nursing Administration and Workforce Management

AI integration within healthcare organizations significantly impacts nursing administration by supporting staffing optimization, workload forecasting, quality improvement, and documentation management.

5,1 Workforce Planning and Staffing Optimization

Nurse staffing shortages and burnout pose global challenges. AI-assisted workforce tools analyse variables such as historical census trends, acuity, weather patterns, seasonal surges, and emergency department inflow.

These systems:

- Reduce overtime and agency costs
- Improve assignment equity
- Predict workload fluctuations
- Enhance nurse scheduling satisfaction
- Optimize skill mix allocation (Carayon et al., 2021)

Hospitals using ML-based staffing models report improved retention and reduced burnout through more consistent workload distribution.

5.2 Workflow Optimization and Operational Efficiency

AI supports administrators in identifying bottlenecks such as:

- Excessive wait times
- Inefficient handoffs
- Medication delivery delays
- Bed turnover delays
- Transport inefficiencies

Computer vision and NLP aid in operational surveillance, identifying patterns invisible through traditional quality improvement methods (Hoefer et al., 2022).

5.3 Electronic Documentation and Administrative Automation

Clinical documentation consumes approximately 35%–50% of nurses' work time. AI tools such as automated speech recognition (ASR), predictive text, and semantic documentation assistance reduce this burden. Speech-to-text systems and predictive text can reduce

documentation time by 20–30% (Shah et al., 2021). Large language models may further improve nursing documentation through auto-drafting, though accuracy validation is essential. Nurses report increased satisfaction and more time for direct patient care.

5.3.1 Impact on Documentation Time

Studies show AI-enabled documentation reduces time spent charting by 20–30% (Shah et al., 2021).

Nurses report increased satisfaction and more time for direct patient care.

5.3.2 AI-Augmented Triage Documentation

NLP-generated triage summaries improve accuracy and consistency of histories.

5.3.3 Administrative Applications

AI automates:

- Inventory management
- Supply chain prediction
- Credentialing reminders
- Staffing compliance checks
- Email sorting and routing

This allows nurse managers to focus on leadership rather than administrative overload.

6. AI in Nursing Research

Nursing research increasingly relies on complex data sources, making AI indispensable for data management, analysis, and interpretation.

6.1 Big Data and Predictive Modeling

Nurse researchers now analyse:

- Electronic health records (EHRs)
- Wearable sensor data
- Home monitoring systems
- Social determinants of health
- Genomic and biometric data

ML supports identification of patterns that traditional statistics cannot detect (Shickel et al., 2018).

6.1.1 Predictive Research Applications

AI-based research has uncovered new risk factors for:

- Falls
- Delirium
- Pressure injuries
- Heart failure exacerbation
- COPD exacerbations
- Sepsis progression

These findings inform practice guidelines and clinical decision support.

6.2 NLP in Qualitative and Mixed Methods Research

Qualitative nursing research traditionally relies on time-intensive manual coding. NLP enables:

- Thematic extraction from interview transcripts
- Sentiment analysis of patient narratives
- Rapid coding of open-ended survey responses
- Pattern discovery in nurse documentation

  (Ford et al., 2016)

NLP accelerates research without replacing human interpretation.

6.3 Simulation-Based Research

AI-powered simulation supports experimental research on:

- Decision-making
- Team communication
- Crisis management
- Clinical judgment under pressure

Virtual standardized patients provide a controlled but dynamic environment for testing educational interventions.

6.4 Ethical Challenges in AI Research

Research challenges include:

- Variable data quality
- Lack of transparency in ML methods
- Limited replicability
- The risk of "automation bias" in interpretation
- Need for interdisciplinary collaboration

7. Nurses' Attitudes, Acceptance, and Readiness for AI

Systematic reviews report that nurses express cautious optimism about AI, believing it can reduce workload and enhance patient safety (Joo & Liu, 2021). Yet concerns persist regarding job displacement, depersonalization, and ethical risks.

AI literacy is strongly associated with positive attitudes and readiness for adoption (Farokhzadian et al., 2021). Incorporating AI competencies into nursing curricula is therefore essential.

7.1 Positive Attitudes

Nurses appreciate AI that:

- Reduces documentation burden
- Identifies deterioration early
- Supports safer medication administration
- Enables greater focus on patient care
- Provides consistent education and reminders

Many nurses view AI as a potential partner rather than threat (Joo & Liu, 2021).

7.2 Concerns and Barriers

Top concerns include:

- Fear of job displacement
- Threats to compassionate care
- Data privacy risks
- Bias in predictions
- Dehumanization of care
- Lack of training
- Overreliance on automated systems

Nurses often express fear of losing autonomy to opaque algorithms.

7.3 Importance of AI Literacy

AI literacy is a major predictor of readiness. Nurses with training in clinical informatics or digital health show higher acceptance, lower fear, and better ability to critique AI recommendations (Farokhzadian et al., 2021).\

8. Ethical, Legal, and Professional Issues

AI raises profound ethical concerns in healthcare. These must be addressed to ensure patient safety, protect human dignity, and safeguard professional integrity.

8.1 Privacy, Data Protection, and Confidentiality

AI systems require enormous datasets that include:

- Vitals
- Diagnoses
- Medication records
- Genomic profiles
- Behavioural patterns
- Social determinants of health

Risks include:

- Unauthorized access
- Secondary use without consent
- Reidentification of "anonymous" data
- Surveillance concerns (Vayena et al., 2018)

8.2 Algorithmic Bias and Equity

Biased data = biased algorithms.

Obermeyer et al. (2019) demonstrated racial bias in a widely used clinical risk prediction tool, underestimating risk for Black patients.

In nursing, bias may influence:

- Fall risk predictions
- Sepsis alerts
- Staffing assignments
- Triage recommendations
- Pain assessment interpretation

Bias undermines equity and amplifies existing disparities.

8.3 Explainability and Transparency

Nurses must understand the rationale behind AI recommendations to ethically integrate them into care.

Black-box models hinder:

- Professional accountability
- Informed consent
- Patient trust
- Legal defensibility (Morley et al., 2020)

8.4 Automation Bias and Overreliance

Automation bias occurs when clinicians trust AI recommendations blindly—even when inaccurate.

This risk is heightened in:

- High-acuity environments
- Understaffed units
- Settings with heavy cognitive burden

8.5 Impact on the Nurse–Patient Relationship

Technology can enhance or erode human connection depending on implementation.

Concerns include:

- Reduced eye contact
- Over-focus on screens
- "Cold" interactions
- Loss of empathy
- Patient perception of being "monitored, not cared for" (Turale & Nantsupawat, 2021)

9. Strategies for Safe and Effective Integration of Artificial Intelligence in Nursing

Integrating AI into nursing practice requires intentional planning, governance, and continuous evaluation. While the benefits are significant, achieving them sustainably depends on structured strategies that prioritize safety, ethics, equity, and nurse empowerment (Table 2).

Table 2. Key Challenges in Implementing AI in Nursing

Challenge Area	Specific Issues in Nursing Context	Implications for Practice
Data quality & bias	Incomplete or biased nursing documentation; under-representation of groups	Biased predictions; inequitable care
Transparency & explainability	Black-box models difficult to interpret at bedside	Reduced trust; reluctance to act on AI advice
Workflow integration	Poorly timed alerts; multiple interfaces	Alert fatigue; increased cognitive load
Professional identity	Fear of replacement; erosion of autonomy	Resistance to adoption; moral distress
Privacy & surveillance	Continuous monitoring of patients and staff	Ethical concerns; regulatory risk
Education & literacy	Limited AI knowledge among nurses and educators	Misuse, overreliance, or rejection of AI
Governance & liability	Unclear responsibility when AI advice is followed or ignored	Legal uncertainty; hesitant use

9.1 Human-Centered and Nurse-Led Design

Nurses are often excluded from early AI design, resulting in poor usability and misalignment with clinical workflows.

Human-centered design (HCD) ensures:

*   Systems align with nursing logic
*   Alerts match real workflow patterns
*   Data visualization supports rapid interpretation
*   Recommendations respect nursing autonomy
*   Ethical concerns are integrated from the start (Cresswell & Sheikh, 2021)

AI development teams should include:

*   Bedside nurses
*   Nurse educators
*   Nurse informaticists
*   Nurse ethicists
*   Patient advocates

9.2 Workforce Education and AI Literacy

AI literacy emerges as one of the strongest predictors of acceptance and safe use (Farokhzadian et al., 2021).

Education should include:

*   Understanding ML/AI fundamentals
*   Identifying algorithmic bias
*   Interpreting risk scores
*   Recognizing automation bias
*   Ethical/legal foundations
*   Data privacy and security
*   Limitations of current AI systems

Nursing schools should integrate AI competencies into curricula, while healthcare organizations should offer continuing education.

9.3 Governance, Regulation, and Ethical Oversight

Healthcare systems should establish AI ethics boards and rigorous evaluation frameworks (Morley et al., 2020). AI governance is essential to ensure transparency and accountability.

Components of effective governance include:

*   AI oversight committees
*   Model validation protocols
*   Bias evaluation processes
*   Documentation standards
*   Incident reporting pathways
*   Compliance audits
*   Patient communication plans

Regulation from bodies such as the FDA and European Commission is evolving rapidly to classify high-risk AI tools (Morley et al., 2020).

9.4 Continuous Monitoring, Evaluation, and Quality Assurance

AI systems must be monitored for performance drift, inequities, and unintended consequences (Krittanawong et al., 2021).

Monitoring should examine:

*   Accuracy and false-alarm rates
*   Impact on nurse workload
*   Clinical outcomes
*   Usability problems
*   Equity and fairness
*   Nurse satisfaction and trust
*   Patient experiences

Feedback loops must allow nurses to flag issues quickly.

9.5 Emphasizing Augmentation over Replacement

AI works best when framed as a tool that augments, not replaces, nursing competencies.

Key messages:

*   AI enhances pattern recognition - not clinical judgment
*   AI improves efficiency—not empathy
*   AI automates the routine—not relational care
*   AI informs decisions—but does not dictate them

Nurse leaders must reinforce that AI is a "second brain," not a substitute for professional expertise.

10. Future Directions for AI in Nursing

AI in nursing is evolving rapidly. Several emerging trends are likely to transform practice even further in the coming decade.

10.1 Multimodal AI Models

Future systems will integrate multiple data sources:

*   EHR data
*   Continuous monitoring devices
*   Bedside cameras
*   Wearable sensors
*   Genomic profiles
*   Patient-reported outcomes
*   Environmental sensors

Multimodal AI offers richer contextual insights, improving prediction accuracy and personalization.

10.2 Large Language Models (LLMs) at the Point of Care

LLMs like GPT-5 and medical foundation models will support:

• Rapid draft documentation

• Patient education summaries

• Triage decision-support

• Clinical guideline synthesis

• Real-time translation for multilingual care settings

Rigorous validation is required to prevent hallucinations or misinformation.

10.3 AI for Personalized Patient Engagement

Future AI systems will deliver tailored interventions based on:

• Literacy level

• Cultural background

• Learning preferences

• Disease-specific patterns

• Behavioural data

This personalization could improve adherence and outcomes.

10.4 Expansion of AI in Low-Resource and Global Health Settings

Mobile-based AI systems have enormous potential for:

• Remote monitoring

• Community health support

• Early detection of outbreaks

• Emergency triage

• Home-based chronic disease management

However, issues of digital equity must be addressed.

10.5 Strengthening Ethical and Professional Standards

AI ethics will become a core component of nursing professionalism. New guidelines will address:

• Algorithmic fairness

• AI transparency

• Patient consent

• Digital trust

• Ethical triage

International organizations (e.g., WHO, ICN) are already developing global AI nursing standards.

Conclusion

Artificial intelligence is reshaping nursing at a depth and scale unparalleled in recent history. From clinical decision support to immersive education, from predictive analytics to workload optimization, AI tools offer remarkable potential to enhance patient safety, reduce nurse burden, and improve care quality. However, the integration of AI into nursing practice carries equally profound ethical, relational, and professional implications.

AI systems can amplify disparities if not designed equitably; they can undermine trust if not transparent; and they can impair relational care if not implemented thoughtfully. For AI to truly augment nursing practice, nurses must be empowered as co-designers, evaluators, and ethical stewards of AI technologies.

A successful future depends on:

• Robust governance

• Continuous evaluation

• Comprehensive AI literacy

• Interdisciplinary collaboration

• Patient-centered design

• Protection of human dignity

Ultimately, AI should not replace the human essence of nursing, but rather enhance it—strengthening nurses' ability to provide compassionate, safe, equitable, and evidence-based care.

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EYE TATTOOING, A FACIAL EXTRA PACK, AND ENHANCED BEAUTY

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Abstract

This article explores the history of various techniques that have been used to improve the aesthetic look of the eye, with associated risks, and it has evolved further recently.

It focuses on its perceived importance, motivations, and potential health implications. This topic has recently gained increasing attention and trend, particularly within younger populations who view such procedures as forms of self-expression and aesthetic enhancement.

The article highlights the cosmetic appeal of scleral tattooing, often linked to individuality, identity and social influence. However, despite its visual impact, eye tattooing carries significant medical and ethical concerns. The procedure involves injecting pigment into the sclera, which can result in serious complications such as inflammation, infection, chronic pain, photophobia, and even permanent vision loss. Given the lack of medical regulation and professional oversight in many cases, these risks are especially pronounced in younger individuals who may not fully understand the long-term consequences.

By exploring both the aesthetic motivations and the medical dangers, the aim is to promote awareness, encourage responsible decision-making, and support the need for public education and stricter safety regulations regarding cosmetic ocular procedures.

Eye or cornea tattooing, also known as keratopigmentation (KTP), is a cosmetic procedure designed to alter eye colour permanently. It can be considered a discipline within cosmetic dermatology, as, according to those choosing the procedure, it enhances facial beautification, boosts confidence, and refines external beauty, focusing mainly on improving the aesthetic balance of the face, which is pursued with a range of procedures , such as fillers, Botox, and chemical peels.

Originally, eye tattooing was used for medical purposes to treat corneal opacities and visual defects. KTP has gained popularity for purely aesthetic reasons. Techniques range from traditional needle-based methods to advanced femtosecond laser-assisted approaches, which are more precise but still carry risks.

Reported side effects of keratopigmentation range from minor issues, such as light sensitivity or localized infection, to more severe problems, including pigment displacement, corneal injury, and, in rare cases, permanent vision impairment. The newer trend, "Lumineyes," utilizes a laser to depigment brown eyes, revealing the underlying blue tones. However, this can block eye drainage, causing glaucoma and blindness.

Historically, altering eye colour has been explored through drops, implants, and lasers—none of which are risk-free or widely approved. Silicone iris implants, for instance, have caused severe harm and have been banned in several countries. Despite their aesthetic appeal, especially under the influence of social media, most eye health professionals strongly warn against such procedures. The long-term safety of eye tattooing remains unknown, particularly in young patients who may later develop complications such as undetected eye diseases or challenges with surgeries like cataract removal.

Ultimately, tattooing the eyes for cosmetic purposes is not recommended. It risks damaging the eye's natural function and obscuring future diagnoses—all for the sake of an unnatural, often idealised appearance.

Keywords: Eye tattooing, eye colouring, eye lasering, eye pigments

Introduction

Keratopigmentation, also known as corneal tattooing, is a surgical procedure used mainly in blind and disfigured eyes when surgical correction is not suitable, by depositing pigments in the corneal stroma, to boost self-esteem, acceptance and confidence. It was considered to be safe and efficacious (1,6,7).

Eye tattooing is quite an intimidating term, as the mantra with any tattoo implies a skin, not the eyes themselves. So, how did all this come along, and what exactly is it implying? Eye tattooing is also known as Laser your eyeballs or Lumineyes, and all doesn't come cheap. However, there have been various efforts to change eye colour for solely cosmetic reasons (1).

Many humans are not satisfied with their personal presentation , and we witness this everywhere, starting with body contouring, tummy tucks, buttock and breast augmentation, lip fillers, and faces constructed by Botox. Recently, this has extended to changing eye colour for merely cosmetic reasons, and permanently, with whatever science brings, without applying logical thinking, beyond the immediate artifice. So, what is this trend we are witnessing nowadays.

The whole story seems to have started with patients suffering from disfiguring corneal opacities, to whom Keratopigmentation (KTP) was applied to mitigate and improve them. KTP is corneal tattooing that has been used for cosmetic management of corneal opacities for centuries, and it's not a new thing (1).

Cornea facts:

* Damage to the cornea can result in scarring, loss of clarity, and reduction in vision.
* The cornea has the highest density of nerve endings of any tissue in the whole body, which acts as a protective mechanism.
* Loss of cornea sensitivity results in increased risks of trauma and poorer healing responses.
* Corneal burns can be caused by chemicals, acids or alkali; however, the latter are farmore severe. Also, thermal burns, heat, and light (flash burns), including UV light, can be detrimental.

The practice of altering the cornea with pigments is not new; records from antiquity describe it was used to hide corneal scars. By the 5th century, Aetius and others experimented with staining techniques involving natural substances (1-2). Interest declined for centuries until the late 19th century, when Von Wecker developed a more systematic approach that included the use of cocaine anaesthesia and specially designed instruments for ink delivery(1).

Taylor later used bundles of needles. In 1901, Nieden developed a tattooing tool like a fountain pen. Armaignac added a small funnel fixed to the cornea, filling it with China ink and tattooing with a needle to create a round, pupil-like effect.

KTP has been used to treat glare from iris loss, trauma, or aniridia, reduce photophobia, and manage intractable diplopia. It's also helpful in improving cosmetic appearance in blind or sighted eyes and has been applied in limbal dermoids. Despite modern contact lenses and surface reconstruction, KTP remains a useful option for those intolerant to lenses or at risk of corneal grafts (1-3).

Traditional techniques use dye after epithelial removal, but it can cause pain, colour fading, and perforation. Intrastromal methods offer better outcomes but still pose risks. Femtosecond laser-assisted KTP is a newer, safer method with improved precision and cosmetic results (1).

The process, in simple terms, means permanently changing the cornea from clear to opaque, which covers the natural iris colour inside (3).

Lumineyes, turn brown eyes blue with new laser technology, brown eyes hide blue pigment underneath; it is as simple as that. So, it is depigmenting of the iris, and thus, brown eyes become blue. So, in simple terms, the person who wishes this procedure walks in with their natural born colour eyes, and leaves with brand-new baby blue eyes.

It has serious sequelae; however, most are downplayed unknowingly.

Pigments:

When KTP was in its infancy , various pigments were used, but it's limited now (Figure 1). The pigments used include Indian ink, organic colours, Chinese ink, animal uveal pigment, platinum chloride, and even soot. CE mark (Conformit Europ ene) pigments are made up of a variety of materials, such as lactic acid, propanediol, and other micronized minerals. These pigments have various colours, such as black, green, and brown (3).

A commonly performed method today is manual intralamellar keratopigmentation, in which a small corneal pocket is created and filled with pigment to achieve the desired colour change (3).\

Many patients undergoing KTP for medical reasons have visual issues, not cosmetic concerns. Some studies suggest using a surgical marking pen over a peripheral iridotomy to let patients preview the post-KTP cosmetic

Figure 1: the technique of KTP

cosmetic result. If acceptable, KTP can proceed. The procedure begins by creating a corneal pocket at a thickness of 40–50%. A radial incision is then made using a diamond knife, followed by intralamellar and circumferential dissection to the blade's full depth. Pigment is injected into the corneal tunnel using a 27-gauge needle. The number and size of incisions depend on the iris defect. This technique is safe, quick, and well-tolerated (3).

Keratopigmentation (KTP) includes several techniques (Figure 1). **Superficial manual KTP (SMK),** the earliest method, uses a needle to puncture the cornea and deposit pigment, but is now rarely used, except for small defects. **Superficial automated KTP (SAK)** uses a device to micro-puncture the anterior stroma to 120 μm, allowing better pigment volume and cosmetic effect. Both use topical or peribulbar anaesthesia. **Femtosecond laser-assisted KTP (FAK)** is a newer, precise technique utilising a laser to create one or two stromal tunnels for pigment injection (1-3). It is reported to be safe, precise, tolerable, and easier to perform based on tunnel formation and good healing, plus ensuring no history of corneal or retinal damage as the suction can worsen their integrity and cause holes and tears (8). It improves both cosmetic and visual outcomes, especially in light-coloured eyes, and is safer with fewer complications than earlier methods.

Cosmetic KTP is used merely to improve the appearance of disfiguring corneal opacities or uneven eye colour, which can impact a person's confidence and quality of life. Today, various corneal tattooing techniques are available to permanently correct these aesthetic concerns. These methods help restore a more natural look to the eye by masking colour changes. In some cases, individuals also seek corneal tattooing purely for cosmetic reasons, aiming to enhance or change their natural eye colour. This elective option is growing in popularity among those wanting a subtle or significant eye colour change without the use of lenses or surgery (3).

Complications of such procedures are commonly classified by the time of the occurrence into intraoperative and postoperative events. Intraoperative complications mainly include perforation, corneal melting, corneal infections, epithelial erosions, dye leakage into the conjunctival space or anterior chamber, and any surgical malpractices (technical mistakes)(4). Whereas, late-onset complications consist of light sensitivity, inconsistent dyeing of the opacity, fading of pigments, uveitis, corneal oedema, conjunctivitis, epithelial defects, and any visual field limitations (4).

The complications of KTP are classified into organic and functional complications. The toxicity of the pigments and their durability have been one of the main concerns.

Visual field limitation, light sensitivity, and MRI alterations are considered functional complications. Change in colour, colour fading, and neovascularization are described as organic complications. Potential risks of KTP include corneal perforation, toxic reaction to pigment, microbial infection, and undesirable migration of pigment (4).

There are mixed opinions about MRI safety after KTP.

Concerns have been raised about the interaction between certain pigments and MRI, particularly when metallic elements are present. While a handful of reports describe image distortion or discomfort during scans performed shortly after the procedure, other investigations have not confirmed significant safety problems (3).

A rare complication of KTP is granulomatous keratitis, often linked to multiple stromal punctures. This condition involves stromal infiltration and a granulomatous response around the pigment, even without any infection by bacteria, fungi, or viruses, indicating a non-infectious inflammatory reaction to the procedure (3). Additionally, any foreign body insertion would have its implications, whether soon or in the years to come, which is currently unknown (3).

The created colour layer can obscure the underlying ocular pathology, and yet people still choose risky eye colour-changing procedures for identity and self-esteem, influenced by culture and social media, despite the blindness risks (4). While commercial growth speeds innovation, many treatments lack proven safety. Young patients face future surgery challenges, and hidden eye diseases may go unnoticed, causing serious harm, like cataracts and other eye issues (4).

In simple terms, even if the laser worked, it would likely cause glaucoma in almost everyone. The eye works like a kitchen sink — the ciliary body acts like a tap, producing fluid, and the trabecular meshwork is the drain that clears it. The laser would release pigment into this flow, clogging the drain and causing pressure to build up, leading to glaucoma and likely vision loss (4). Additionally, the iris is a very vascular organ and can bleed leading to the rise in the pressure inside the eye (4).

Each elective cosmetic surgery has an estimated cost of $6000 per eye, and some people opt for mismatched eye colours (heterochromia iridis), which costs $ 12000 (3).

Historical evolution of eye colour changes (Tables -1 and 2): it's not new, though (3).

1-   During the Second World War (WWII), unethical experiments were carried out on concentration camp prisoners in an attempt to alter eye colour, including the use of drug-based drops which was called project eye colour (Projekt Augenfarble). These trials, led by Nazi physicians, caused suffering without producing any meaningful results. Magnussen's post-war publication attempts were blocked due to ethical concerns (1-2).

2-   Since 1996, prostaglandin eye drops for glaucoma, like Latanoprost® and Bimatoprost®, have been known to darken the iris, especially in light-coloured eyes. This occurs due to increased melanin. Older adults and some ethnicities, like Japanese individuals, are more affected. No eye colour-changing products exist yet, though lash-enhancing versions do (3).

3-   Since 2011, unapproved eye drops like iColour claim to lighten eye colour using N-acetylglucosamine, which may reduce melanin. However, this effect isn't proven in iris cells. These products lack FDA or CE approval, raising safety concerns like infections, inflammation, allergic reactions, or even retinal damage, risking vision loss (3).

4-   Iris implants, originally designed for medical use, became popular for cosmetic reasons. The NewColorIris implant, launched in 2006, caused severe complications like glaucoma and blindness, leading to its removal from the market. Its successor, BrightOcular, also lacks FDA/CE approval and continues to cause similar issues, despite ongoing global use. Having said this, silicone iris implant surgery is not widely recommended due to potential complications, corneal decompensation, uveitis, and glaucoma, leaving some patients nearly blind. Such a procedure can be considered malpractice and should be discouraged (3).

5-   Laser treatments to turn brown eyes blue gained attention in 2011. Q-switched Nd: YAG lasers are now claimed to be the most effective, though not fully proven. These non-approved procedures target iris melanin but can cause serious issues like uveitis and pigmentary glaucoma, sometimes resulting in permanent vision damage (3).

6-   Keratopigmentation, or corneal tattooing, dates back nearly 2000 years to Galen of Pergamon, who used it to mask corneal opacities. Modern techniques began in 1869. Today, it's used medically for light sensitivity or iris defects. Recently, interest has grown in using it purely to change eye colour cosmetically. Keratopigmentation uses different methods. Traditional techniques, based on Von Wecker's method, insert pigment into superficial corneal layers using manual or automated needle punctures. Complications include colour fading, perforation, and uveitis. Modern methods use femtosecond lasers to create stromal pockets for pigment injection, offering more precision but still carry risks. Intrastromal keratopigmentation complications include corneal perforation (less with femtosecond lasers), infection, neovascularisation, allergic reactions, pigment migration, colour changes, and visual issues. Third-generation mineral micronized pigments, like CE-marked Biochromaeyes®, cause fewer pigment-related problems than older pigments such as Indian ink or animal uveal pigment (3)

Conclusion

Corneal tattooing has existed for nearly 2,000 years and can be used therapeutically and cosmetically (8). Since 2011, iris implants and lasers have become the most commonly used tools to make that dream a reality for those who want a permanent change in eye colour.

Intrastromal keratopigmentation carries risks like infection, pigment migration, and vision problems. It is often driven by identity and self-esteem (3). Since most patients are young, long-term issues may appear later. Patients may overlook future issues, especially with cataract surgery. The pigment can also mask eye diseases. Despite its appeal, this cosmetic procedure poses both short- and long-term risks to eye health. Although the technique shows promising results in patients with ocular pathology, there is little research and, lack of standardization on the use of keratopigmentation for purely cosmetic procedures on healthy eyes, while exploring its safety(5). Changing eye colour in healthy eyes for strictly cosmetic reasons is a risky procedure to take. Procedures can cause grim complications, missed eye diseases, and problems with future surgeries. These risks may lead to irreversible damage, vision loss, or even loss of the eye, and in rare cases, threaten life itself. Also, tint fading and corneal neovascularization can be a possible problem(6).

Table 1: summary of eye colouring:

Contact lenses	Various other methods, drops, laser, tattooing
Safer option when used properly	Iris implants often banned and riskier
Temporary and disposal	Permanent and controversial with unknown long-term safety
• can pose some risks, particularly when used improperly or for extended periods. These risks include • infections • corneal problems • irritation	• Potential dangers include: • Glaucoma (increased eye pressure) and potential blindness • Uveitis (eye inflammation) • Vision loss or damage • Uneven eye colour • Corneal damage • Photosensitivity

Table 2: different techniques utilised

Different techniques	Possible and raised complications
Eye drops containing adrenaline were used in WWII; prostaglandin drops used in glaucoma since 1996	It caused increased iris pigmentation
Commercial drops, 2011	Not effective and dangerous
Iris implants, 2011	Corneal decompensation, uveitis, and glaucoma, banned and removed as it left patients blind
Commercial laser, 2011, to make brown eyes blue	Possible complications are anterior uveitis, and pigmentary glaucoma
Modern intrastromal keratopigmentation	Complications include cornea perforation, bacterial infection, allergic or toxic reaction to pigmentation, migration of pigment, functional complications like visual filed limitation, and light sensitivity, obscure ocular pathology of the cornea or iris

The bottom line is it's not recommended unless future studies prove it's safe. Most eye experts strongly warn against it.

So, the lingering question is whether it is worth the risk at all, where the demander is insecure about their natural eye colour, and what is the future health of those eyes, as there aren't many extensive studies yet, and there is a lack of data about its safety?

Also, we know albino patients who have pigment deficiency, are sensitive to light. Do those eyes' pupils dilate at all and respond to the natural light? Also, what about those with blue eyes who want dark eyes? All the evidence raised and the clinical studies published make it clear that KTP offers today an excellent option for the corneal surgeon, providing acceptable functional and cosmetic outcomes in cases of only disabled corneas, irregular pupils, or traumatic iris injuries, which can be performed using different procedures (1,4). Moreover, I am wondering if those providers took the chance, and had tried the procedure in the first place themselves to be the role model for their claimed safe procedure to have your dream eye colours, as some promote heavily on social media multiple platforms, and risk their sight, their most important sense in the world, to see and appreciate. Anyone who wants to use that technique should be vigilant and weigh the benefits against the risks. After all, it is all based on self-acceptance, and loving your inborn eyes, which is your unique identity, and not photocopying aliens, which is the basis of the cosmetic industry when it comes to lip fillers and the Botox used, creating distorted, obsessed nations.

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