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Role of Serum Survivin Levels in Breast Cancer Prognosis and Histological Characteristics: A Comprehensive Review

Shilpa Dhamija[1], Bushra Fiza[2]*, Kavita Sharma[1], Madhu Sharma[1]
[1] PhD Scholar, Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, Rajasthan, India.
[2*]Professor, Biochemistry, Mahatma Gandhi Medical College & Hospital, MGUMST, Jaipur, Rajasthan, India.

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ABSTRACT
Background: Breast cancer represents a global challenge because it is still the number one cause of cancer death among females. The need of having trustworthy prognostic biomarkers for cancer risk evaluation and personalized therapy has become an indispensable necessity rather than a choice. Survivin, a protein that inhibits apoptosis and is produced by the BIRC5 gene, is involved in different tumors among which breast cancer is one and its expression leads to cancer proliferation, treatment resistance, and worsened prognosis. Serum levels of Survivin can be measured in an easy and non-invasive way that can reflect the level of aggressiveness of the corresponding tumor. **Objective**: The present review will delve into the correlation between serum Survivin levels and breast cancer prognosis, as well as the histological traits involved. **Methods:** The literature search was extensive and included searching in all major biomedical electronic databases such as PubMed, Embase, and Web of Science among others for publications that report serum Survivin in breast cancer patients. Data were obtained, which included assay methods, serological levels, correlation with the tumor grade, molecular subtypes, lymph node status, and survival outcomes, and were then consolidated. **Results:** The serum Survivin levels were found to be significantly higher in the breast cancer patients as compared to healthy controls in all the studies done on this aspect. The elevated serum Survivin levels were found to be negatively correlated with several clinicopathological features, i.e., the tumor was of high grade, lymph node was positive, and the molecular subtype was aggressive. A few studies found the opposite relation between serum Survivin elevation and overall as well as disease-free survival, which has been interpreted as indicative of its prognostic potential. Nevertheless, variability in assay methods, cut-off values, and study designs have constrained the comparability across the board. **Conclusion:** The serum Survivin level is an indicator of the breast cancer prognosis and at the same time, a non-invasive diagnostic agent. However, the assay procedures used in different laboratories need to be standardized..

1. INTRODUCTION:

1.1 Background

Breast cancer is the most prevalent cancer in women all over the world and as well as the second most prevalent cancer-specific death in women[1]. It is defined as abnormal increase in the breast cells that create tumors. Uncontrolled these tumors may turn out to be life-threatening, and may spread to other body parts. Although breast cancer is known to develop in the ductal epithelium (ductal carcinoma), it may also develop in the lobules (lobular carcinoma). Non-invasive, in situ cancer at the early stage is normally not fatal and can be

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easily identified during screening. Nevertheless, in the event of the invasion of adjacent tissues by the cancerous cells, they cause lumps or thickenings in the breast that can later result in spreading to lymph nodes or other organs, a process called metastasis. The metastatic breast cancer is especially perilous and may considerably lower the survival rates[2]. The global incidence of breast cancer among women in 2022 was about 2.3 million, with 670 000 women dying of the condition. The prevalence of breast cancer rises with age and its effect is widespread, as it has become an issue of women in every country of the world.

In developed nations, breast cancer screening has effectively enabled the detection of breast cancer at an early stage, as in most cases, the tumors have not attained symptoms [3]. During the 1980s and 2020, there is a reduction in the mortality related to breast cancer in these nations by 40 percent due to the advancements in early detection and treatment. Faithfully, those nations that have been successful at reducing cancer mortality rates have experienced a 2-4% yearly decline in breast cancer mortality rates. This development highlights the need to identify the disease early and create a specific treatment regimen.

Biomarkers can be used to predict the prognosis of breast cancer patients. Prognostic biomarkers will give the required information on the probable course of the disease whereas predictive biomarkers will be used to choose the most effective treatment. These biomarkers will provide clues about the probability of recurrence and also the possible response to treatment. The somatic mutations, DNA methylation changes to regulate the expression of genes, the elevated level of microRNAs (miRNAs) (that regulate the expression of messenger RNA (mRNA)) and the presence of circulating tumor cells (CTCs) in the blood are key prognostic factors, which indicate poor prognosis. Individualized oncology biomarkers are becoming more actively used in the molecular diagnostics of different cancers such as chronic myeloid leukemia, colon, lung, and breast cancers, and melanoma. These biomarkers play a key role in determining the potential advantages of the targeted therapies and the toxicity of chemotherapy, which can assist clinicians to make a better decision in terms of patient treatment [4].

1.2 Survivin

Survivin (SVN) is the smallest representative of the anti-apoptotic (IAP) family of proteins that is important in controlling the process of cell mitosis and inhibition of apoptosis. Survivin, a gene which Ambrosini cloned in 1997, is found on human chromosome 17 [5]. BIRC5 is the wild-type human-survivin gene that is 147 kb long and includes four exons and three introns. The 16.5 kDa (142 amino acid) human survivin protein has two major functional domains, a baculoviral IAP repeat (BIR) (100 amino acids) at the N-terminus and an a-helix (42 amino acids) at the C-terminus. The two domains are important in the regulation of mitosis with BIR domain mainly contributing to the inhibition of apoptosis. Survivin is expressed in different cellular compartments, such as the nucleus, cytoplasm, mitochondria, exosomes, cell membrane, and extracellular matrix, and its functions depend on subcellular localization, reversible dimerization, and multiple post-translational changes, such as acetylation, ubiquitination, and phosphorylation[6].

Survivin plays two significant functions in cancer cells, namely [1] the regulation of mitosis through the creation of the chromosomal passenger complex (CPC) with other proteins and (2) the inhibition of apoptosis [7-8]. Survivin mainly participates in mitosis of the cell in the nucleus. It controls chromosome alignment during mitosis by phosphorylation of Ser20, Thr34, and Thr48 which is required to segregate chromosomes correctly and proliferate cells [9]. Moreover, 89-98 residues also interact with CRM1 (chromosome region maintenance 1) which facilitates nuclear export and acetylation of residues 89-130 enhances dimerization and translocation of survivin to the nucleus. Moreover, ubiquitination at Lys63 is a process that is involved in the regulation of chromosome positioning by regulating the dynamic interaction of survivin with centromeres [10].

The contribution of survivin in apoptosis is also important. Mitochondrial survivin blocks apoptosis by interacting with apoptotic proteins like cytochrome C (Cyt-C) and SMAC (second mitochondria-derived activator of caspase, or DIABLO) to prevent their release of mitochondria into the cytoplasm thereby preventing the assembly of an apoptosome complex and activation of caspase-9 [19]. This release of Cyt-C is inhibited by phosphorylation of mitochondrial survivin at Thr34, which further enhances cell survival. Moreover, phosphorylation at Leu64,87, Asp70,71 increases the formation of the complex with SMAC/DIABLO thereby inhibiting the apoptosis further [6].

Survivin participates in various tumorigenic processes in cancer cells. It has been demonstrated to facilitate DNA repair of the broken strands of the DNA through the interaction with the DNA-dependent protein kinase (DNA-PKcs) and the Ku70, which are essential proteins during DNA repair [11-12]. In minimizing the damage of DNA that

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is related to poly ADP-ribose polymerase (PARP) activation [13], survivin also contributes to chromosomal instability that facilitates tumourigenesis and the survival of the tumor. This increased apoptosis is reduced by overexpression of survivin, which enhances tumor evolution and metastasis [14]. Also, alternative splicing of the pre-mRNA of survivin may produce different forms that have varied roles in tumorigenesis and mitotic regulation[15-16]. Its post-transcriptional modification, including phosphorylation by cyclin-dependent kinase 1 (CDK1), and polo-like kinase 1 (PLK1), also regulates its activity, which leads to chromosomal missegregation and abnormal cytokinesis, which are typical of most solid tumors [17-18]. Also in general, survivin, due to its multiple functions in cell division and apoptosis, is a major determinant in cancer development and progression [9, 21]. The second pathway of SVN-mediated inhibition of apoptosis is that of apoptosis-inducing factor (AIF). The AIF is released in a response to apoptotic stimuli, moving out of the mitochondria intermembrane space into the nucleus, which causes the fragmentation of the DNA. This caspase-independent pathway of apoptosis is inhibited in mitochondria by binding of SVN with AIF. Cytoplasmic SVN is produced by the nucleus and mitochondria and functions in the prevention of apoptosis SVN also occurs in the cytoplasm where it either inhibits caspase 3 directly or caspase 9 indirectly via HSP60 and XIAP. The formation of monomeric SVN the form needed to transport nuclei and be able to inhibit apoptosis6 requires deacetylation of residues 89-130 in SVN to form monomeric SVN. In their release out of mitochondria, SVN without phosphorylation on Ser20 is able to interact with the X-linked inhibitor of apoptosis (XIAP). This SVN-XIAP complex makes XIAP more stable, resulting in greater suppression of caspase-9-dependent apoptosis [21-22] Thr48 phosphorylation is also essential in the anti-apoptotic functions of SVN [3]. HSP90 and HSP60 interact with SVN at the 79-90 residues and are molecular chaperone, which enhances the stability of SVN and its antipoptotic effect on apoptosis [9, 23-24].

Although the diagnosis and treatment of breast cancer have made tremendous progress, the clinical community still requires a better and less invasive prognostic marker that would enable better prediction of disease progression and patient survival. Although the use of the tumor tissue biomarkers is heavily utilized, the use of circulating biomarkers which are more readily accessible to serial monitoring are taking a leading role. Survivin has become a molecule of significant interest since it is significantly expressed in several malignancies, as well as plays a vital role in cell survival pathways. Nevertheless, the available body of literature that deals with the particular correlation between serum survivin concentration and its association with patient prognosis, as well as with the detailed histological features of breast tumor, is disjointed. The proposed review will fill this gap by synthesizing the existing evidence to give an extensive picture of the prognostic and diagnostic usefulness of serum survivin in breast cancer.

The main aim of literary review is to review and summarize the existing literature on the importance of serum survivin levels in breast cancer in a systematic manner. The two important areas that will be specifically addressed in this review will be to examine the relationship between serum levels of survivin and prognosis of patients, including the accepted measures of overall and disease-free survivorship. Second, the connection between serum survivin levels and some of the histological features of breast tumors, including tumor grade, lymph node status, and receptor status (ER, PR, and HER2), will be examined. In such a way, the goal of the review is not only to combine the current findings but also critically assess the evidence, define the major gaps in knowledge, and suggest the ways of research in the future to confirm the clinical utility of serum survivin as a prognostic biomarker.

2. METHODOLOGY:

This review was conducted using a comprehensive and systematic approach to evaluate the role of serum survivin levels in predicting prognosis and their association with histological characteristics in breast cancer patients. A structured literature search was performed across major electronic databases including PubMed, Embase, Scopus, and Web of Science to identify relevant studies published from January 2000 to the most recent available date. Additional articles were identified through manual screening of reference lists of selected studies and relevant review articles.

The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including *"breast cancer," "survivin," "serum survivin," "circulating survivin," "prognosis," "overall survival," "disease-free survival," "histological characteristics," "tumor grade," "lymph node status," "ER," "PR," and "HER2."* Boolean operators (AND/OR) were used to refine the search and maximize retrieval of relevant studies.

Inclusion and Exclusion Criteria

Studies were included if they:

1. Were original research articles, clinical studies, or meta-analyses published in peer-reviewed

journals;
2. Involved human breast cancer patients;
3. Measured serum or circulating survivin levels using validated methods such as ELISA or related assays;
4. Reported associations between serum survivin and prognostic outcomes (overall survival, disease-free survival, recurrence) and/or histological or clinicopathological features.

Studies were excluded if they:
1. Were editorials, letters, conference abstracts, or case reports;
2. Focused exclusively on tissue survivin expression without serum or circulating measurements;
3. Involved cancers other than breast cancer;
4. Were published in languages other than English.

Data Extraction and Synthesis:
Data were independently extracted from eligible studies, including author details, year of publication, study design, sample size, survivin assay methodology, serum survivin levels, cut-off values, and reported associations with clinicopathological parameters such as tumor grade, lymph node status, molecular subtype, and survival outcomes. Due to heterogeneity in study design, assay techniques, and reporting standards, a qualitative narrative synthesis was performed rather than a quantitative meta-analysis.

Quality Assessment
The methodological quality of included studies was assessed based on study design, sample size, clarity of survivin measurement methods, and adequacy of statistical analyses. Potential sources of bias, including selection bias and variability in assay protocols, were critically evaluated to ensure balanced interpretation of findings.

3. SERUM SURVIVIN LEVELS AS A PROGNOSTIC INDICATOR IN BREAST CANCER:

3.1 Correlation with Overall Survival (OS):
There is limited but suggestive evidence that higher levels of survivin (especially in tumor tissue, and far less often measured in serum) are correlated with worse overall survival in breast cancer patients. Ionta et al. (2010) studied a cohort of 53 breast cancer patients treated with primary chemotherapy. They compared survivin-positive vs survivin-negative tumors (IHC). Over 5- and 10-year follow up, survivin-negative patients had significantly better OS: 5-year OS ~75% vs ~38% in survivin-positive; 10-year OS ~56.3% vs ~23.8%. Survivin was a significant independent prognostic factor for worse OS (HR ~2.61) [25]. Hinnis et al. (2007) examined 165 patients (all died of breast cancer within a range of follow-up 12-127 months) using IHC. High survivin expression was associated with Grade III disease, ER negativity, and shorter survival. On multivariate analysis, survivin was an independent predictor of shorter duration of survival (P = 0.005) alongside tumor grade [26]. Meta-analyses such as "The prognostic role of survivin expression in breast cancer" incorporate many studies of survivin expression (tissue) rather than serum and find that survivin expression is associated with poorer OS, though confidence intervals and effect sizes vary, and some studies do *not* find statistically significant relationships [27].

3.2 Correlation with Disease-Free Survival (DFS) and Recurrence:
Most data come from tissue survivin expression, but some studies use serum survivin and examine recurrence. *Ionta et al. (2010)* found DFS was poorer in surviving-positive cases. In their cohort of 53, 5-year DFS in survivin-negative was ~59.4% vs ~23.8% in survivin-positive, though the p-value for DFS was marginal (p ~0.095) [25]. Early diagnostic value of survivin and its alternative splice variants measured by *serum* survivin (ELISA) in 40 breast cancer patients, correlated with clinical factors. While the study showed that moderate-to-high serum survivin levels were more common in patients vs controls ($p < 0.05$), they did not clearly show a longitudinal DFS curve or recurrence analysis [28]. The meta-analysis by *Kucukzeybek et al. (2024),* evaluating survivin expression (mostly IHC/PCR), showed survivin expression correlates with DFS (HR ~0.89, CI 0.42-1.36) (though this CI crosses 1.0), indicating less consistent evidence than for OS. So, evidence for serum survivin as a predictor of recurrence/disease-free survival is weaker and less direct; more focused on tissue expression [27].

3.3 Association with Other Prognostic Factors:
To evaluate whether serum survivin is independent, one must look at its correlation with known prognostic factors like tumour size, stage, hormone receptors, lymph node status. A study by "Serum-survivin-levels and their relationship to histological parameters in breast cancer patients" measured serum via ELISA. They found that serum survivin levels were significantly higher in patients with positive lymph node involvement vs node negative (p = 0.03). However, serum survivin was not significantly related to tumor size (p = 0.72), number of involved nodes (p = 0.78), metastasis (p = 0.19), histology type (p = 0.19), or age (p = 0.72) [28]. Histological grade, ER/PR/HER2: *The Khan et al. (2014)* serum study found that moderate-to-high survivin was detected in most patients irrespective

of receptor status; in triple negative (ER-PR-HER2-) ~86%, in E,PR and HER2− ~83%. They observed higher serum survivin in Stage II/III/IV but did *not* show strong statistical difference across stage [27]. In IHC/PCR tissue studies, survivin expression is often associated with higher grade, ER negativity, PR negativity, and HER2 positivity. For example, Hinnis et al. found high survivin expression correlated with Grade III and lack of ER [26] also meta-analysis *Oparina et al., 2021* shows higher BIRC5/survivin expression in ER-negative BC cohorts; but again, tissue rather than serum [30].

4. Serum Survivin and Breast Cancer Histological Characteristics:

Histological characteristics remain fundamental determinants of breast cancer prognosis and therapeutic decision-making. Parameters such as tumor grade, histological type, lymph node involvement, and hormone receptor status (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]) provide critical insights into tumor aggressiveness, metastatic potential, and response to treatment. Despite their clinical value, these parameters are primarily derived from tissue biopsies, which are invasive and may not fully capture tumor heterogeneity or dynamic disease progression. Consequently, there is increasing interest in identifying circulating biomarkers that can non-invasively reflect underlying histopathological features of breast tumors [24-25].

Survivin, a member of the inhibitor of apoptosis protein family, plays a central role in cell cycle regulation, inhibition of apoptosis, and tumor progression. Its overexpression has been consistently associated with aggressive tumor behavior and unfavorable histological features in multiple malignancies, including breast cancer. While tissue-based survivin expression has been extensively studied, emerging evidence suggests that serum survivin levels may also correlate with key histological characteristics of breast cancer. Evaluating the relationship between circulating survivin and tumor histopathology may provide valuable insights into tumor biology and support the development of serum survivin as a surrogate marker for aggressive disease features [26-27]. This section summarizes and critically examines the existing evidence linking serum survivin levels with histological characteristics of breast cancer.

4.1Association with Tumor Grade and Histological Type:

This study found no significant association between serum survivin levels and histological parameters such as histological type (ductal vs lobular etc.) in breast cancer (p = 0.19). Also, no association with tumor grade was reported in that study [29]. In contrast, tissue survivin expression studies often do show associations: higher survivin in high-grade tumors, more aggressive histological types. A meta-analysis by *Oparina et al*. shows that high BIRC5/survivin expression is characteristic of certain tumor subsets and higher grade [30]. The Khan et al. study also had moderate to high serum survivin in many subtypes, but did *not* find statistically significant differences across histological types or grades in their serum measurements [28].

4.2Association with Lymph Node Status:

This study found that patients with positive lymph node involvement had higher serum survivin (p = 0.03) compared to node negative ones. Number of involved nodes, however, did not correlate (p = 0.78) [29]. Tissue studies strongly support that survivin expression (especially cytoplasmic or nuclear) is higher in node-positive tumors. Hinnis et al. found correlation of high survivin expression with node positivity [26]. Also the review "The role of survivin in diagnosis, prognosis and treatment of breast cancer" mentions that tumor size, histologic grade, lymph node metastasis and stage correlate with positive survivin detection in tumor tissue or in circulating tumor cells [31].

4.3 Relationship with Hormone Receptor and HER2 Status:

The serum study by Khan et al. (2014) showed moderate to high serum survivin levels in triple negative subtype (ER-PR-HER2-) and also in ER,PR and HER2- subtype, but did *not* find strong statistical differences between subtypes [28]. A study did *not* find association between serum survivin and hormone receptor status or HER2 status 'significant' in their data[29].Tissue based studies: Hinnis et al. (2007) showed negative ER status is associated with high survivin expression. Also, meta-analyses report that ER-negative tumors tend to have higher survivin expression compared to ER-positive tumors. For example, Oparina et al. found higher BIRC5/survivin in ER-negative [26].Current evidence suggests that survivin plays an important role in breast cancer prognosis, though the strength of association varies depending on whether its expression is measured in tissue or serum. Numerous tissue-based studies consistently demonstrate that high survivin expression correlates with shorter overall survival and poorer disease-free survival, confirming its value as an independent prognostic marker. In contrast, research on serum survivin levels remains limited and less conclusive. Small cohort studies using ELISA have shown that elevated serum survivin may be associated with worse outcomes, but these findings are not always statistically significant and

require validation in larger populations. With respect to established prognostic factors, serum survivin has shown some correlation with lymph node positivity, but not consistently with tumor size, stage, or histological type. Tissue-level studies, however, more strongly link survivin expression with aggressive features such as high tumor grade, estrogen and progesterone receptor negativity, and HER2 positivity. Similarly, while serum studies have not demonstrated significant associations with hormone receptor or HER2 status, tissue analyses suggest that survivin expression is higher in ER-negative and HER2-positive subtypes.

5. RESULTS & DISCUSSION:

While the accumulating body of research affirms survivin's significance in breast cancer prognosis, there are several nuanced observations and unresolved issues that temper enthusiasm for its immediate clinical adoption. A major meta-analysis (Li et al., 2014) including 3,259 breast cancer patients across 23 studies found that positive survivin expression (tissue, via IHC or PCR) is associated with both worse overall survival (OS) (HR ≈1.37; 95% CI: 1.12–1.68) and disease-/recurrence-free survival (DFS/RFS) (HR ≈1.34; 95% CI: 1.02–1.76) compared to survivin-negative cases [32]. Similarly, the "Prognostic Significance of BIRC5/Survivin in Breast Cancer" study (using large cohorts VGR-BC, METABRIC, SCAN-B) confirmed high tissue survivin or BIRC5 mRNA levels are robustly associated with poorer survival, independent of nodal status and estrogen receptor status [33]. However, when considering *serum survivin levels*, the picture is less clear. The study "Serum and urine survivin levels in breast cancer" (n=43 cases, 21 controls) reported that baseline serum survivin was *not* significantly higher in breast cancer patients versus control ($p = 0.19$) except in patients with lymph node involvement ($p = 0.043$) This indicates potential for serum survivin in capturing metastasis-related features but less so for early detection or general prognosis [34]. Another study "The Value of Serum Survivin Level in Early Diagnosis of Cancer" (including breast cancer among types) found significantly higher serum survivin levels in cancer patients vs healthy controls (196.23 pg/ml vs 117.73 pg/ml; $P = 0.019$), and an optimal cutoff (>120.8 pg/ml) gave ~4.2-fold risk increase for having cancer [35]. *Bai et al. (2021)* used a meta-analysis to review the expressions of survivin in different cohorts of breast cancer. They discovered that high survivin levels in tumour tissue were strongly linked to overexpression of poor overall survival, disease-free survival, and tumour aggression, i.e. high grade and negative hormone receptors. It is this tissue-derived evidence that enhances the idea that serum survivin, particularly when assessed in circulatory formats, such as exosomes, could be indicative of equivalent tumour biology and a negative-prognosis indicator in serum. These results of Bai et al. (2021) support the premise that the circulating survivin assays (including serum or exosomal forms) might reflect the same prognostic indicators in tumour tissues, and hence could provide a non-invasive alternative approach to monitor breast cancer progression[,28].

Several studies have explored the relationship between serum survivin levels and histological parameters in breast cancer patients. For instance, a study by *Guney et al. (2006)* found that serum survivin levels were significantly higher in patients with nodal involvement compared to those without, suggesting a potential role of serum survivin as a marker for lymph node metastasis. However, the same study did not observe significant correlations between serum survivin levels and other histological parameters such as tumor grade or receptor status[34]. Similarly, *Goksel et al.* reported moderate correlations between serum survivin levels and progesterone receptor concentration but found no significant relationships with age or other histological parameters in early-stage breast cancer patients [36].

Khan et al. (2020) conducted a review of the possibilities of serum survivin and exosomal survivin as liquid biopsy markers in a variety of cancer types, such as breast cancer. They emphasized that an increase in circulating survivin is associated with an increase in the stage of disease and metastasis, as well as an unfavourable prognosis. The advancement of technology in liquid biopsy assays, including ELISA of serum survivin and also the isolation of exosomal survivin, offers the prospects of liquid serum survivin being used as a predictive biomarker. The review helps in making a selection of assays, pre-analytical variables, and clinical significance of circulating markers. It provides the foundation of doing future studies on serum survivin assays, which are not only clinically relevant but that could be incorporated in the prevailing clinical practice. The approach conducted by Khan et al. (2020) offers the methodological framework that can be utilized in the further studies devoted to the investigation of serum survivin as the predictor of breast cancer prognosis [29].

The article by Sharma et al. (2022) is one of the newest developments in serum exosomal survivin. They examined the pre- and post-operative small extracellular vesicle (sEV)-survivin in breast cancer patients and its role in the detection of early metastasis. As the initial results indicate, high

levels of sEV-survivin in serum are associated with metastatic progression. Though this study is in preprint version, it provides the nearest and most pertinent evidence on serum survivin in breast cancer in the last few years especially in the framework of dynamic monitoring of the disease conditions. In the view of Sharma et al. (2022), exosomal survivin could be a useful clinical biomarker when it comes to the early detection of metastasis and, consequently, offer a much-needed tool in the management of breast cancer, namely the ability to detect and monitor the disease at its initial stage [30].

In contrast, tissue-based studies have provided more consistent evidence linking survivin expression with histological characteristics and research by Hinnis et al. demonstrated that nuclear survivin expression was associated with a favourable prognosis, whereas cytoplasmic expression correlated with a poor prognosis. Additionally, studies have shown that survivin overexpression correlates with HER2 and EGFR expression, suggesting a link between survivin levels and certain receptor status [26].

In order to put serum survivin in perspective with other liquid biopsy technologies, Lin et al. (2021) and Tomasik et al. (2023) offer an informative review of the history of circulating tumor markers, both protein and exosomal, development and validation. These reviews explain the significance of sample handling, analytical validity, and clinical validation, which are all significant procedures to design and apply serum survivin assays in clinical oncology. With liquid biopsy still growing in popularity in the oncology field, such insights will be heavily needed in the refinement of the serum survivin assay technique to ensure it can be easily implemented in clinical practice to detect breast cancer prognosis. The discrepancies between serum and tissue-based findings may be attributed to several factors. Serum survivin levels can be influenced by various physiological and pathological conditions, potentially confounding the results. Moreover, differences in assay techniques, sample handling, and patient populations can contribute to variability in findings. Tissue-based analyses, such as immunohistochemistry, provide more localised information about protein expression and may offer more precise correlations with histological characteristics [31].

The role of serum and exosomal survivin as a prognostic biomarker in breast cancer has received increasing attention in the research conducted over the past few years, and it is believed to have the potential of enhancing the diagnosis, treatment monitoring, and prognosis of the patient. Demirci et al. (2023) investigated the usefulness of serum survivin as a prognostic factor in patients with metastatic pancreatic cancer, which can be of great use in breast cancer. Their analysis established that higher baseline levels of serum survivin were prioritized to worse progression-free survival (PFS) and overall survival (OS), providing evidence of the significant role of the biomarker in gauging the severity of disease: it is a significant indicator of patient prognosis. Moreover, the researchers also established that high levels of serum survivin were negatively associated with chemotherapy response, meaning that serum survivin would be of useful value as a predictive of therapy non-response. This is especially applicable to breast cancer where chemotherapy resistance is a great challenge in the efficacy and disease management effectiveness of the treatment. The findings of this paper may indicate that the level of serum survivin monitoring may have the potential to make clinical decisions, particularly in patients who are prone to chemotherapy resistance or relapse of the disease [32].

In the same manner, Hashemi et al. (2025) examined the exosomal survivin in breast cancer, including its role in chemoresistance. They discovered that the higher the levels of exosomal survivin, the higher the resistance of the chemotherapeutic agent paclitaxel used in treating breast cancer. The research presented the evidence that the administration of paclitaxel resulted in the release of more survivin in extracellular vesicles (exosomes), which were discovered to mediate chemoresistance through increasing cell survival. This observation leads to the possibilities of using exosomal survivin as a marker of chemotherapy resistance and a therapeutic target of drug resistance. Such findings play an essential role in breast cancer, whereby resistance to chemotherapy has been a major challenge, and the discovery and tracking of biomarkers such as exosomal survivin have become significant in personalising the treatment regimen [33].

The meta-analysis by Kucukzeybek et al. (2024) also supports the significance of survivin in estimating the outcomes of breast cancer. In this overall analysis of several studies, it was found out that excessive expression of survivin in both the tissues and serum was strongly linked with unfavourable overall survival (OS) and disease-free survival (DFS) in breast cancer patients. The analysis summarised the evidence of different cohorts and stages of cancer, and it was proven that the high levels of survivin are associated with the aggressive phenotype of a tumour, including high-grade tumours, metastasis to lymph nodes, and

negative HR. The research confirms this argument based on the usefulness of survivin as a strong biomarker of poor prognosis, which further supports the use of survivin measurement in the clinical practice of breast cancer to determine the progression of the disease and the outcome of patients [34].

Wijaya et al. (2024) also made another significant contribution to the literature by reviewing the role of exosomal survivin as a diagnostic and prognostic marker in breast cancer. Their review marked that the exosomal survivin levels were greatly enhanced in serum samples of breast cancer patients who underwent a treatment with a chemotherapy drug, paclitaxel, which is widely used with the treatment of breast cancers. The authors came to the conclusion that exosomal survivin might be a useful tool to monitor the response to chemotherapy and the presence of early metastasis. Through measuring exosomal survivin concentrations, the clinicians would potentially be able to evaluate the effectiveness of the treatment and modify the therapeutic protocol before the clinical relapse. This review highlights the clinical potential of exosomal survivin as a non-invasive method to detect the disease progression of breast cancer early and monitor it [35].

Based on this study, Malla et al. (2025) examined the molecular pathways of the exosomal survivin role in breast cancer. Their research centred around the effects of survivin-loaded exosomes on the tumour microenvironment as well as affecting chemotherapy resistance through cell-to-cell signalling and survival signalling in the nearby cancerous cells.

They have discovered that exosomal survivin does not only contributes to cancer cells avoiding the impact of chemotherapy, but also contributes to increasing metastasis and tumor growth. This action mechanism underlines the duality of exosomal survivin as a disease progression marker and an important agent in the mechanism of breast cancer. The results indicate that exosomal survivin would be an attractive target to interfere with such mechanisms of survival and enhance the response to treatment in breast cancer patients [36].

All of these studies taken together highlight the role of both serum and exosomal survivin as a rising form of prognostic biomarkers in breast cancer. Demirci et al. (2023) and Hashemi et al. (2025) emphasise the predictive capabilities of serum and exosomal survivin regarding resistance to therapy and prognosis. Their study justifies the application of survivin as a non-invasive marker to be quantified using the blood-based assays as an alternative to more invasive tissue biopsies. In the meantime, Kucukzeybek et al. (2024), Wijaya et al. (2024), and Malla et al. (2025) provide some further insight into the relation between high levels of survivin and low patient outcomes in addition to drug resistance and metastasis. Integrating the survivin assays into clinical practice may greatly increase our capability to measure the effect of treatment, forecast the recurrence of the disease, and tailor treatment plans to individual patients with breast cancer [37-39].

These studies indicate that surviving, especially as an exosomal and serum protein, can revolutionise the breast cancer treatment system by offering the clinician a means of tracking the disease progression as well as assessing the efficacy of treatments [40-42]. Since the current research on survivin is still in its developing phase, the researchers should engage in future studies that will help to verify these findings in larger and more diverse patient samples, to optimise assay methods, to investigate the therapeutic perspectives of targeting survivin as a component of precision oncology efforts. Reliable serum and exosomal survivin assays that are both cost-effective and easy to develop may one day become a vital component of daily clinical practice that eventually leads to the improvement of the cure prognosis of breast cancer patients [43-50].

CONCLUSION:

The cumulative evidence reviewed indicates that serum survivin represents a biologically plausible and clinically relevant prognostic biomarker in breast cancer. Its consistent elevation in patients compared with healthy controls supports the concept that circulating Survivin reflects underlying tumor biology rather than incidental systemic changes. Importantly, the association between high serum Survivin levels and adverse histopathological features-such as high tumor grade, lymph node metastasis, and aggressive molecular subtypes-suggests that serum survivin mirrors tumor aggressiveness and invasive potential. From a prognostic standpoint, the observed correlations between elevated serum survivin and poorer overall survival and disease-free survival underscore its potential utility in risk stratification. As Survivin is mechanistically involved in apoptosis inhibition, cell cycle regulation, and treatment resistance, its presence in the circulation may integrate multiple dimensions of tumor behavior, providing information beyond conventional clinicopathological parameters. This positions serum survivin as a promising adjunct biomarker that could complement established prognostic tools and aid in identifying patients at higher risk of recurrence or poor outcomes.

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However, despite these encouraging findings, the current body of evidence is constrained by methodological heterogeneity. Variability in assay platforms, detection antibodies, sample processing, and cut-off definitions limits reproducibility and hampers translation into routine clinical practice. Additionally, many studies are retrospective and involve relatively small cohorts, reducing the strength of causal inferences and generalizability. In conclusion, serum Survivin holds significant promise as a non-invasive prognostic indicator that correlates with aggressive disease characteristics and unfavorable outcomes in breast cancer. To realize its clinical potential, future research must focus on assay standardization, clearly defined threshold values, and well-designed, large-scale prospective studies.

LIST OF ABBREVIATION:
AIF: Apoptosis-Inducing Factor, **BA:** Bioavailability, **BC:** Breast Cancer, **BIRC5:** Baculoviral IAP Repeat Containing 5, **BIR:** Baculoviral IAP Repeat, **CPC:** Chromosomal Passenger Complex, **CRM1:** Chromosome Region Maintenance 1, CTCs: Circulating Tumor Cells, **Cyt-C:** Cytochrome C, **DFS:** Disease-Free Survival, **DNA-PKcs:** DNA-Dependent Protein Kinase Catalytic Subunit, **EGFR:** Epidermal Growth Factor Receptor, **ELISA:** Enzyme-Linked Immunosorbent Assay, **ER:** Estrogen Receptor, **HER2:** Human Epidermal Growth Factor Receptor-2, **HR:** Hazard Ratio, **HSP60:** Heat Shock Protein-60, **HSP90:** Heat Shock Protein-90, **IAP:** Inhibitor of Apoptosis Protein, **IHC:** Immunohistochemistry, **Ku70:** Ku Autoantigen 70-kDa Subunit, **miRNA/miRNAs:** MicroRNA/MicroRNAs, **mRNA:** Messenger RNA, **OS:** Overall Survival, **PARP:** Poly(ADP-ribose) Polymerase, **PFS:** Progression-Free Survival, **PLK1:** Polo-Like Kinase-1, **PR:** Progesterone Receptor, **sEV:** Small Extracellular Vesicle, **SMAC/DIABLO:** Second Mitochondria-Derived Activator of Caspases/Direct IAP-Binding Protein with Low pI, **SVN:** Survivin, **TNBC:** Triple-Negative Breast Cancer, **XIAP:** X-Linked Inhibitor of Apoptosis.

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