"IMMUNOHISTOCHEMICAL EXPRESSION OF LAMININ 332 IN TRIPLE NEGATIVE BREAST CANCER: A CROSS SECTIONAL STUDY"

BY

DR. KAMALA K, **MBBS**

DISSERTATION SUBMITTED TO

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN PATHOLOGY

UNDER THE GUIDANCE OF

DR. KALYANI R , MD, PhD, FAMS, FICP

PROFESSOR AND FORMER HOD

DEPARTMENT OF PATHOLOGY

SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH TAMAKA, KOLAR, KARNATAKA

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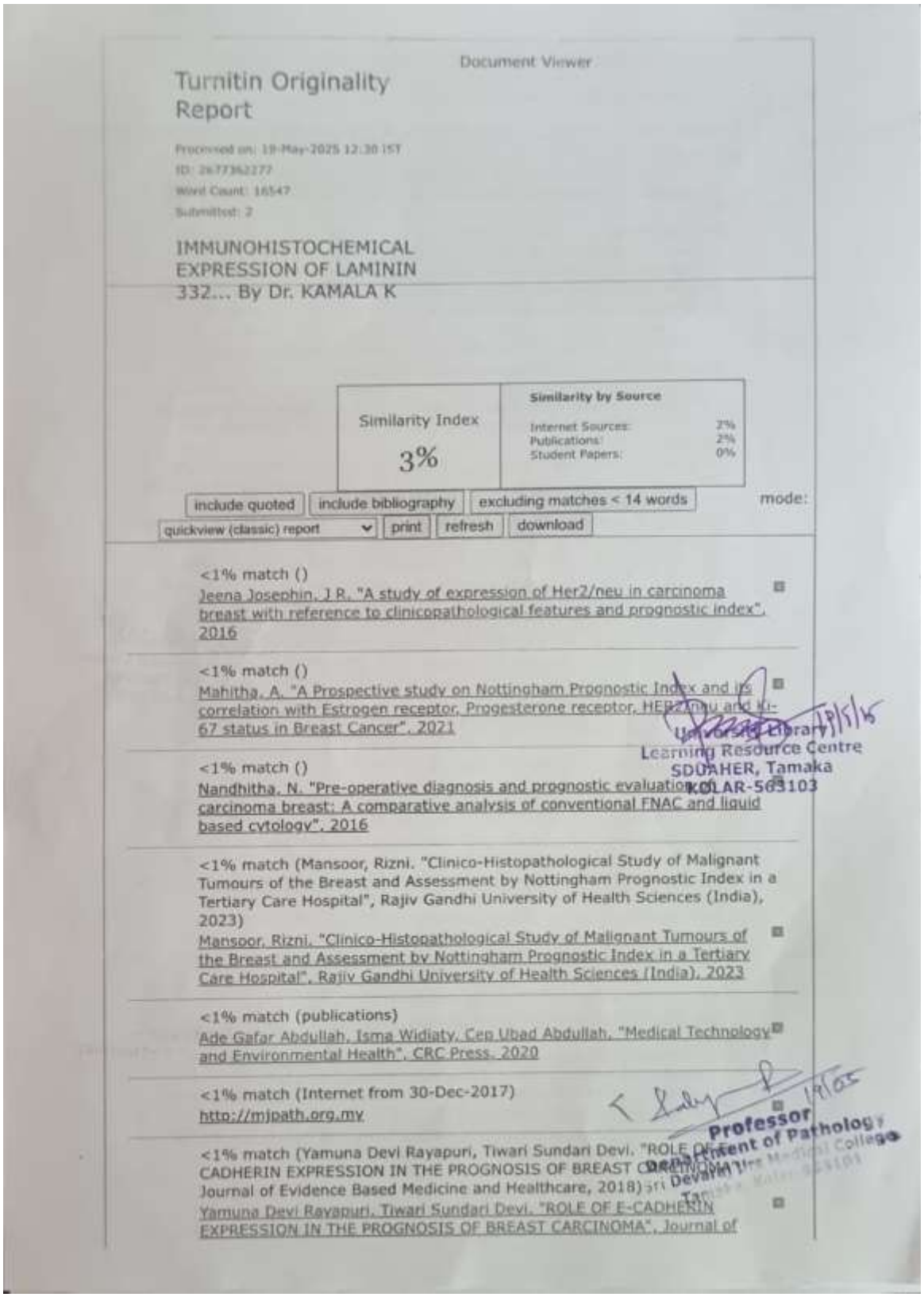

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ABSTRACT Background: BC is MC cancer among females, constituting 11.7%. It represents leading cause of mortality among females. High prevalence of malignancy among developed/developing nations presents a significant global threat. TNBC thought to be more dangerous having worse results than other types of BC. Laminin is a glycoprotein that plays several roles in cancer progression, including cell proliferation, invasion, metastasis, and EMT. Most of TNBC patients have a BL phenotype with LM 332 overexpression. Post chemotherapy TNBC recurs because of metastatic potential. In TNBC patients 70% have LM 332 which is associated with bad end results following treatment. OBJECTIVES AIM: To evaluate the role of Laminin 332 expression in triple negative breast carcinomas. OBJECTIVES: 1) To asses IHC expression of LM 332 in TNBC. 2) To study the association of Laminin 332 expression with age, histological type, grade, and stage of TNBC. MATERIALS AND METHODS: All TNBC patients received from Department of Surgery at RLJH and Research Institute to the Department of Pathology associated with SDUMC, Tamaka, Kolar between January 2019 and September 2024 was considered for study. Both prospectively, retrospectively were considered. The data and paraffin blocks was collected from archives of Pathology departrment. Following histopathological parameters TNBC cases were carefully studied and Laminin 332 Immunohistochemistry (IHC) was performed as per the Standard operating procedures (SOP's) of the department. Association of IHC expression of Laminin 332 and histopathological parameters was studied. RESULTS: Among 50 TNBC cases, 26 (56%) are >50 years. Majority of patients i.e.23 (46%) are grade 3 carcinomas, 46 (92%) cases had Infiltrating Duct Carcinomas (IDC), 39 (78%) had LVI ,46 (92%) were without PNI and 22(44%) had high grade TILS. All the TNBC cases exhibited positivity for either Laminin 332 IHC score 5 (64%) and Laminin 332 IHC score 6 (36%). Laminin 332 IHC Score 5 (71.8%) was associated with presence of LVI and laminin IHC Score 6 (p Value 0.041) 7(63.6%) associated with absence of LVI which was important as per statistical corelation (p Value 0.041). Present study as per statistical analysis no association was found among IHC score 5/6 and age group, post menopausal, parity, BMI , tumour size , grade, laterality, pT stage, nodal stage, TNM stage, NPI , PNI, TILS. CONCLUSION: TNBC exhibit aggressive behaviour and are associated with unfavourable clinicopathological outcomes. Laminin immunostaining may serve indicator of prognosis for assessing post treatment results in TNBC. Utilizing laminin antibodies as a potent chemotherapeutic drug can facilitate effective cancer management and enhance patient survival. In this study we documented that all the TNBC patients were positive for Laminin 322, but there was statistically significant association only with LVI. Keywords: TNBC, LAMININ 332, LVI, Infiltrating Duct Carcinomas (IDC), NPI INTRODUCTION BC is the MC cancer among women, constituting 11.7% . It represents leading cause of mortality among females. More prevalence in developed/developing nations presents a significant global threat.1 In 2020, the worldwide incidence of breast cancer was 22,61,419 (11.7%), with 6,84,996 deaths (6.9%). Among females, the incidence rate of BC is a leading source of cancer mortality worldwide.1 In India, BC has recently overtaken cervical carcinoma as the most common cancer among women, a change attributed to the gradual shift in lifestyle factors.1 In India, the GLOBOCAN results in 2020 showed that BC is a significant health challenge, accounting 13.5% in malignancies and 10.6% of cancer- related mortalities. Over all risk stands at

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Date : Signature of the Candidate

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LIST OF ABBREVIATIONS

BC – Breast Carcinoma

TNBC – Triple Negative Breast Carcinoma

LM 332 – Laminin 332

ER – Estrogen Receptor

PR – Progesterone Receptor

Her 2 – Human epidermal growth factor receptor 2

IDC – Infiltrating Ductal Carcinoma

TDLU – Terminal duct lobular unit

WHO – World Health Organisation

AJCC – American Joint Committee on Cancer

H&E – Hematoxylin and eosin

NPI – Nottingham Prognostic index

TBS – Tris buffer Solution

ASCO – American Society of Clinical Oncology

CAP – College of American Pathologists

BRCA1 – Breast Cancer gene 1

MSBR – Modified Scarff Bloom Richardson grading

NOS – Not other specified

CAFs - Cancer associated fibroblasts

SDF-1 - Stromal cell-derived factor

IBC - Invasive breast cancer

ILC - Invasive lobular carcinoma

IHC - Immunohistochemistry

MSL - Mesenchymal stem-like subtype

LAR - Luminal androgen receptor subtype

TME - Tumor microenvironment

TILS - Tumor Infiltrating Lymphocytes

PNI - Perineural invasion

LVI - Lymphovascular invasion

EMT - Epithelial to Mesenchymal Transition

AR - Androgen Receptor

BL-1 - Basal-like 1

BL-2 - Basal-like 2

IM - Immunomodulatory

MSL - Mesenchymal stem-like

EGFR - Epidermal growth factor receptor

STUDY TITLE: IMMUNOHISTOCHEMICAL EXPRESSION OF LAMININ 332 IN TRIPLE NEGATIVE BREAST CANCER: A CROSS-SECTIONAL STUDY

ABSTRACT

BACKGROUND:

Breast carcinoma (BC) is the most common malignancy among women, constituting 11.7% of all cancer cases. It represents the leading cause of mortality among females. The increasing prevalence of disease in both developed and developing countries presents a significant global threat. Triple negative breast cancer (TNBC) is thought to be more aggressive and has a worse prognosis than other types of breast cancer. Laminin is a glycoprotein that plays several roles in cancer progression, including cell proliferation, invasion, metastasis, and epithelial-mesenchymal transition. Many of TNBC cases have a basal-like phenotype with laminin 332 overexpression.

Triple negative breast cancer is more likely to spread distantly and to recur after treatment. Regarding immunohistochemical studies of laminin 332 expression in breast carcinoma, roughly 70% of triple negative breast cancers are positive for laminin 332 and is associated with an unfavourable clinicopathological state and poor prognosis.

AIM AND OBJECTIVES

AIM: To evaluate the role of Laminin 332 expression in triple negative breast carcinomas.

OBJECTIVES:

1) To evaluate Immunohistochemical expression of Laminin 332 in triple negative breast carcinomas.
2) To study the association of Laminin 332 expression with age, histological type, grade, and stage of Triple negative breast cancer.

MATERIALS AND METHODS:

All the cases of triple negative breast carcinoma received from Department of Surgery at RL Jalappa Hospital and Research Institute to the Department of Pathology attached to Sri Devaraj Urs Medical college, Tamaka, Kolar from January 2019 to September 2024 were considered for the study. Both prospective and retrospectively were considered. The data and paraffin blocks were retrieved from the archives of Department of Pathology.

The following histopathological parameters of TNBC cases were carefully studied and Laminin 332 Immunohistochemistry (IHC) was performed as per the Standard operating procedures (SOP's) of the department. Association of IHC expression of Laminin 332 and histopathological parameters was studied.

RESULTS:

Among 50 TNBC cases, 26 (56%) were elderly patients above 50 years of age. A higher proportion of cases i.e.23 (46%) were grade 3 tumours, 46 (92%) cases had Infiltrating Duct Carcinomas (IDC), 39 (78%) had LVI ,46 (92%) were without PNI and 22(44%) had high grade TILS. All the TNBC cases exhibited positivity for either Laminin 332 IHC score 5 (64%) and Laminin 332 IHC score 6 (36%). Laminin 332 IHC Score 5 (71.8%) was associated with presence of LVI and laminin IHC Score 6 (63.6%) associated with absence of LVI which was statistically significant correlation with *p* Value 0.041. Present study there was no statistically significant association between IHC score 5/6 and age group (p =0.803), menopausal status (p =0.774), parity (p =0.688), BMI (p=0.929), tumour size (p=0.813), grade (p=0.450), laterality (p =0.769), pT stage (p=0.656), nodal stage (p=0.254), TNM stage (p=0.294), NPI (p=0.554), PNI (p=0.612) and TILS (p=0.187).

CONCLUSION:

Triple negative breast carcinomas exhibit aggressive behaviour and are associated with unfavourable clinicopathological outcomes. Laminin immunostaining may serve as a prospective prognostic marker for predicting outcomes in patients of triple-negative breast cancer. Utilizing laminin antibodies as a potent chemotherapeutic drug can facilitate effective cancer management and enhance patient survival. In this study we documented that all the TNBC patients were positive for Laminin 322, but there was statistically significant association only with LVI.

Keywords: TNBC, LAMININ 332, LVI, Infiltrating Duct Carcinomas (IDC), NPI

INTRODUCTION

INTRODUCTION

Breast carcinoma (BC) is the most prevalent malignancy among women, constituting 11.7% of all cancer cases. It represents the leading cause of mortality among females. The increasing prevalence of disease in both developed and developing countries presents a significant global threat.[1]

In 2020, the worldwide incidence of breast cancer was 22,61,419 (11.7%), with 6,84,996 deaths (6.9%). Among females, the incidence rate of BC is a leading source of cancer mortality worldwide.[1] In India, BC has recently overtaken cervical carcinoma as the most common cancer among women, a change attributed to the gradual shift in lifestyle factors.[1] In India, the GLOBOCAN data for 2020 reveals that breast cancer (BC) is a significant health challenge, accounting for 13.5% (178361) of all cancer cases and 10.6% (90408) of cancer-related deaths. The cumulative risk stands at 2.81.[1] Approximately one in four women was newly detected and died due to BC in India.[2] The reported prevalence of breast cancer in Kolar is 6.41%. [3] In India, the age-adjusted incidence of BC among females is 25.8 per 1, 00,000 and the death rate is 12.7 per 1,00,000. The proportion of BC in Bangalore is 34.4%.[2] Breast cancer exhibits a significant likelihood of recurrence and metastasis.[4]

TNBC is thought to act more violently and has a more favourable prognosis than other forms of breast cancer. These cancers are distinguished by a lack of ER, PR, and HER2neu gene expression. A large number of these cases having a basal-like appearance with laminin 332 overexpression.[5] According to this study, TNBC spreads more easily distantly and to reoccur following therapy. Laminin is thought to be linked to the basal-like-phenotype and BRCA1 deficiency.[6] This study will also attempt to ascertain its association with lymph node metastasis and TNM staging of TNBC.[7]

Laminin is a heterotrimeric glycoprotein that performs a variety of functions both during embryonic development and in mature tissues.[8] During embryonic development, this extracellular matrix protein mediates cell attachment, migration, and tissue organization.[9] It also aids in cellular differentiation and survival, as well as the growth of embryonic stem cells.[10] Laminin constitutes a part of epithelial and vascular basement membranes within mature tissue, where it aids in the maintenance of cell adhesion and cohesion. Both epithelial and stromal cells secrete Laminin, and it binds to integrin receptors on cell surfaces.[9]

AIMS AND

OBJECTIVES

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OBJECTIVES:

1.To evaluate Immunohistochemical expression of Laminin 332 in triple negative breast carcinomas.

2. To study the association of Laminin 332 expression with age, histological type, grade, and stage of Triple negative breast cancer.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

The breasts are modified sweat glands in both genders but it is primitive in males. In women, it is fully formed post-puberty and accessory organ of the female reproductive system. [11,12]

Development of Breast:

Development of starts at 5th to 6th week of fetal life as two ventral bands. At 9 months, there is a distinct linear elevation, known as, "milk line". The breast ridges extend from the axillary to the inguinal areas.[13] In humans mammary ridges dissolve while the embryo grows. The primary bud formed in breast is as an outcome of in growth of ectoderm and later results in the formation of 15 to 20 secondary buds and then in to branches of lactiferous ducts. Major lactiferous ducts open in to the nipple. Myoepithelial cells seem to originate from basal cells around 23 to 28 weeks of gestational age. They are important in the branching morphogenesis of the mammary gland by synthesizing the basement membrane. The Female breast growth initiates under the influence of estrogen and progesterone during adolescence. These hormones help in the proliferation of connective tissue and epithelial components and also in deposition of fatty tissue. [14,15]

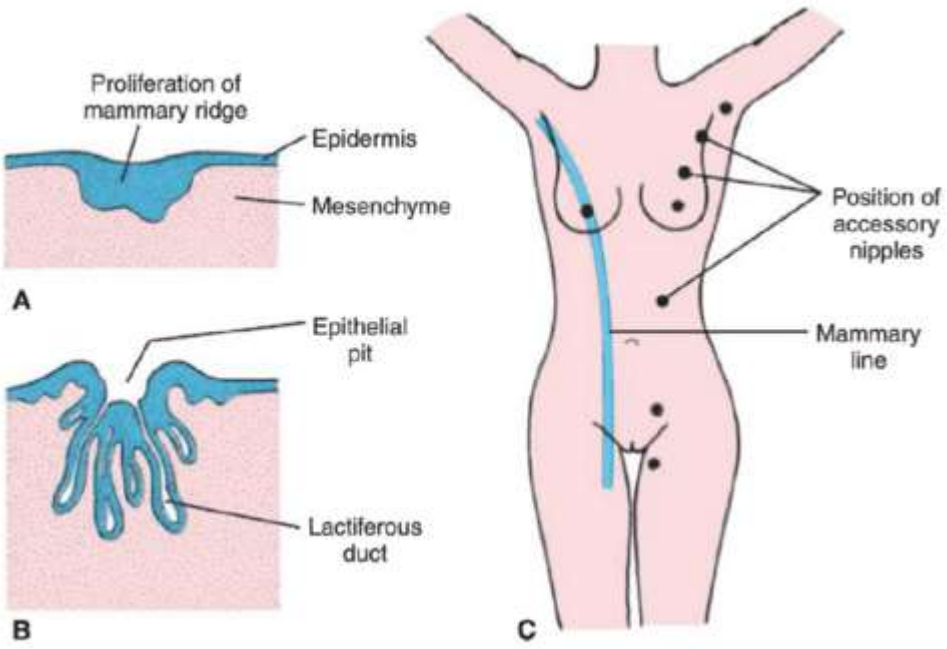


Fig 1 - A and B. Sections of the growing mammary gland at the third and eighth months. C. Positions for accessory nipples (blue line-mammary line).[16]

Gross Anatomy of Breast:

Breast are modified apocrine sweat glands situated on the anterior thoracic wall. It stretches between 2nd - 7th rib and from the midaxillary line's anterior margin to the sternum's lateral margin. "Superolateral quadrant is extended towards the axilla along the inferolateral edge of pectoralis major from which it projects a little and may outspread through the deep fascia up to the apex of the axilla. It lies on the deep pectoral fascia, which overlies pectoralis major and serratus anterior superiorly and external oblique and its aponeurosis inferiorly." The areola possesses a circular morphology and exhibits a size range of approximately 3 to 6 cm, often located at the level of the 4th rib. The epidermis of the nipple and areola is highly pigmented and comprises sebaceous glands that create surface projections, known as the tubercles of Morgagni or areolar glands, which expand during pregnancy, resulting in the tubercles of

Montgomery. The breast parenchyma contains ducts of 15 to 20 lobes, all of which enter the nipple and dilate, forming milk sinuses, bonded together by septa of connective tissue referred to as interlobular connective tissue. Each lobe has a pyramidal shape with a base away from the nipple. The suspensory ligaments, connective tissue band reach out from interlobular connective tissue and gets attached to the dermis.[17,18]

Blood Supply of breast

The arterial supply of the breast is via internal mammary artery, lateral thoracic artery and intercostal arteries. [17,18]

Venous drainage of breast

Venous drainage occurs via perforating branches of the internal mammary vein, tributaries of the axillary vein and the perforating branches of posterior intercostal veins. [17,18]

Lymphatic drainage of breast

About 75% of the lymphatic drainage of the breast is through the axillary lymph nodes. There are approximately 20-30 lymph nodes in the axillary region and these are located lateral, medial, superficial and deep to the pectoralis minor muscle. Superficial lymphatics drains contralateral breast and the anterior abdominal wall. Direct drainage may be there to the supraclavicular (deep cervical) nodes and its involvement is indicative of advanced disease. Lymphatic drainage of the epithelial and mesenchymal components of the breast is the primary route of metastatic spread of breast cancer. [17,18]

Nerve Supply of Breast:

Breast is innervated by lateral cutaneous, anterior cutaneous branches of 2 - 6 intercostal nerves.[17,18]

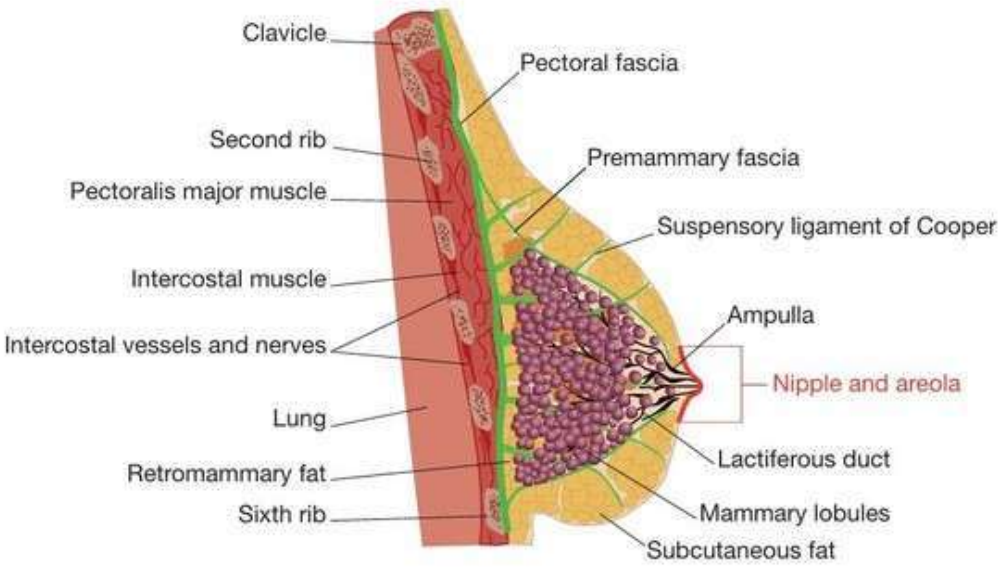


Figure 2: Anatomy of normal breast [19]

Normal Histology of Breast:

The ducts and acini have a bilayered structure consisting of basal myoepithelial cells and a luminal layer of columnar or cuboidal epithelial cells, which have a secretory function. Milk transport from the alveoli through lactiferous ducts is facilitated by the contraction of myoepithelial cells, which form a discontinuous layer around the ducts, whereas near the nipple, the lactiferous ducts are lined by keratinizing stratified squamous epithelium.[20]

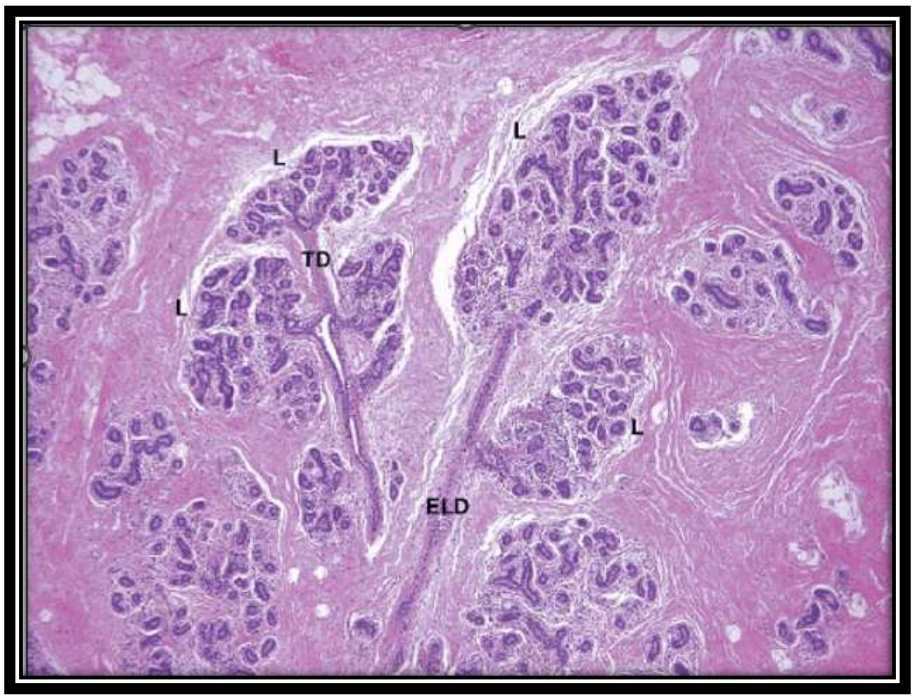


Fig 3: Normal histology of breast

Normal adult female breast tissue showing extralobular ducts (ELD), terminal ducts (TD), and lobules (L), the latter composed of groups of small glandular structures, the acini.[21]

RISK FACTORS: [22]

1. Positive family history

2. Female sex

3. Early menarche

4. Germline mutation of tumour suppressor genes

5. 70 – 80 years is MC age group

6. Hormonal therapy

7. Nulliparous women or females having first child birth after 35years

8. Previous biopsies with benign breast disease with atypical hyperplasia or proliferative changes.

9. Obesity

10. Exposure to radiation

11. Carcinoma of endometrium and contralateral breast having carcinoma

12. Breast feeding for less time than one year

13. Organochlorine pesticides [22]

ETIOPATHOGENESIS: Breast carcinoma arises from clonal expansion of genetically altered cells, influenced by inherited susceptibility genes (e.g., BRCA1, BRCA2, TP53, CHEK2) in approximately 12% of cases, while the majority are linked to hormonal and environmental factors, such as radiation exposure.[4,23,24]

- Age: The risk of breast cancer increases with age, with a lifetime risk of 1 in 8 in the US, varying by age group: 1 in 202 (under 39), 1 in 26 (40-59), and 1 in 28 (60-69), according to SEER data.

- Personal history: A personal history of breast cancer significantly increases the risk of developing a new breast cancer, either in the same breast (ipsilateral) or the other breast (contralateral), with metachronous contralateral breast cancer being a common concern for breast cancer survivors.

- Breast pathology: Proliferative breast disease, including lesions like ductal hyperplasia and intraductal papillomas, increases breast cancer risk 1.5 to 2 times that of the general population.

- Family history: A family history of breast cancer increases a woman's risk of developing the disease.

- Genetic predisposition: About 20-25% of breast cancer patients have a family history, but only 5-10% of cases show autosomal dominant inheritance, indicating a strong genetic link.

- Early menarche: Early menarche increases breast cancer risk, while a 2-year delay in menarche reduces risk by 10%.

- Parity and age at first full-term pregnancy: Nulliparous women (those who have never given birth) have a higher risk of breast cancer compared to women who have had children.

- Breast feeding: Breastfeeding has been shown to reduce the risk of breast cancer, with longer durations of breastfeeding associated with greater risk reduction.

- Age at menopause: Late menopause (after age 55) is associated with a higher risk of breast cancer.

- Hormone replacement therapy (HRT): Hormone replacement therapy (HRT) is associated with an increased risk of breast cancer, particularly hormone receptor-positive tumours.

- Obesity: Postmenopausal obesity is linked to an increased risk of breast cancer.

- Radiation: Exposure to radiation, such as from medical procedures or nuclear events, increases the risk of developing breast cancer.

• Chest wall radiation in childhood cancer treatment increases breast cancer risk in a dose-dependent manner, meaning higher radiation doses lead to a greater risk.[23,24]

MOLECULAR MECHANISM OF CARCINOGENESIS: [24,25,26]

The hypothesis for breast cancer is that; All breast cancers originate from resident breast tissue stem cells. Driver mutation is acquired by these cells first. Then any one of the three main genetic pathways of carcinogenesis that lead to cancer are:

1. The dominant route is associated with chromosomal 16q losses, chromosome 1q gains, and PIK3CA activating mutations. This pathway causes ER-positive and HER2-negative carcinoma.

2. HER2 positive cancers are caused by the pathway linked to HER2 gene amplification.

3. HER2 gene amplification and ER-mediated alterations in gene expression are not necessary for the development of HER2-negative, ER-negative malignancies. [24,25,26]

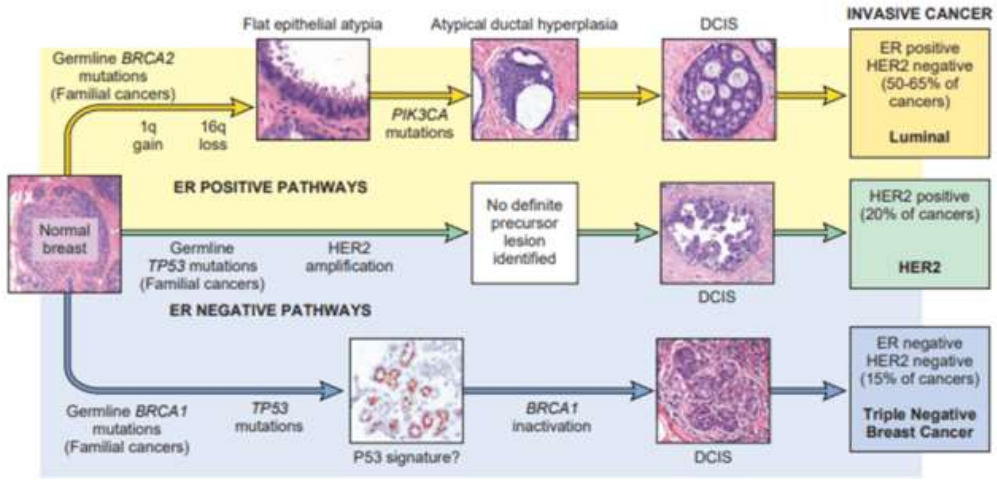


Fig 4: Major pathways of breast cancer development[24]

The box with the question mark suggests that the rapid progression of potential precursor lesions to carcinoma might be the reason why no identifiable precursor lesions have been found.

Molecular Regulation of Carcinogenesis:[24,25,26]

- Chemical carcinogenesis: Chemical carcinogenesis occurs when electrophilic intermediates from substances bind to DNA, forming adducts that can alter proto-oncogenes or tumour suppressor genes. If these DNA changes aren't properly repaired, they can lead to malignant cell transformation.

- Xenobiotics with structural similarities to endogenous chemicals can bind to receptors like estrogen receptors, disrupting normal cellular function and potentially leading to toxicity or cancer through altered gene expression.

- The glucocorticoid receptor and estrogen receptor (ER) ligands influence cellular function through the regulation of gene expression. Structural similarities between xenobiotics and natural chemicals may lead to toxicity or cancer by disrupting normal homeostasis.

- Molecular and cellular signalling that cause carcinogenesis

- Tumours reprogram cellular metabolism to support their growth, often depriving normal cells of nutrients. They also promote angiogenesis, forming new blood vessels to increase oxygen delivery, mediated by factors like vascular endothelial growth factor (VEGF).[25,26]

Clinical features:

Most of the patients with breast cancer present with a vague lump

in the breast, pain or discharge from the nipple. Apart from carcinomas, many other conditions can also present as breast lump such as cysts and fibroadenomas. Even nipple discharge can be associated with benign conditions like galactorrhea. Even, pain which is a common symptom can be associated with cyclical pain and non-cyclical pain can be due to infections or trauma. Hence, it is very important to consider a detailed history and careful examination will aid to the nearest diagnosis.[27]

LOCALISATION:

Breast cancer most commonly arises from the terminal ductal-lobular unit (TDLU), with the upper outer quadrant being the most frequent location (40-50% of cases). Various morphological phenotypes exist, each with distinct clinical and prognostic features.[24,28,29,30]

Table 1: WHO classification of BC 2019[28,29]

EPITHELIAL TUMOURS	
INVASIVE BREAST CARCINOMA	Infiltrating ductal carcinoma not otherwise specified (NOS) Oncocytic carcinoma Lipid rich carcinoma Glycogen rich Carcinoma Sebaceous carcinoma Lobular carcinoma NOS Tubular carcinoma Cribriform carcinoma Mucinous adenocarcinoma Mucinous cystadenocarcinoma NOS Invasive micropapillary carcinoma of breast Metaplastic carcinoma NOS

RARE AND SALIVARY GLAND TUMORS	Secretory carcinoma Acinic cell carcinoma Mucoepidermoid carcinoma Polymorphous adenocarcinoma Adenoid cystic carcinoma Classic adenoid cystic carcinoma Solid basaloid adenoid cystic carcinoma Adenoid cystic carcinoma with high grade transformation Tall cell carcinoma with reversed polarity
NEUROENDOCRINE NEOPLASMS	Neuroendocrine tumour, NOS Neuroendocrine tumour, grade 1 Neuroendocrine tumour, grade 2 Neuroendocrine carcinoma NOS Neuroendocrine carcinoma, small cell Neuroendocrine carcinoma, large cell
EPITHELIAL–MYOEPITHELIAL TUMOURS	Pleomorphic adenoma
NON INVASIVE LOBULAR NEOPLASIA	Atypical lobular hyperplasia Lobular carcinoma in situ NOS Classic lobular carcinoma in situ Florid lobular carcinoma in situ Lobular carcinoma in situ, pleomorphic typical lobular hyperplasia Lobular carcinoma in situ NOS Classic lobular carcinoma in situ Florid lobular carcinoma in situ Lobular carcinoma in situ, pleomorphic
DUCTAL CARCINOMA IN SITU (DCIS)	Ductal carcinoma, non infiltrating, NOS DCIS of low nuclear grade DCIS of intermediate nuclear grade DCIS of high nuclear grade
BENIGN EPITHELIAL	Usual ductal hyperplasia

PROLIFERATIONS AND PRECURSORS	Columnar cell lesions including flat epithelial atypia Atypical ductal hyperplasia
ADENOSIS AND BENIGN SCLEROSING LESIONS	Sclerosing adenosis Apocrine adenoma Microglandular adenosis Radial scar/complex sclerosing lesion
PAPILLARY NEOPLASMS	Intraductal papilloma Ductal carcinoma in situ, papillary Encapsulated papillary carcinoma Encapsulated papillary carcinoma with invasion Solid papillary carcinoma in situ Solid papillary carcinoma with invasion Intraductal papillary adenocarcinoma with invasion
ADENOMAS	Tubular adenoma Lactating adenoma Duct adenoma NOS
MESENCHYMAL TUMOURS	
FIBROBLASTIC AND MYOFIBROBLASTIC TUMORS	Nodular fasciitis Myofibroblastoma Desmoid-type fibromatosis Inflammatory myofibroblastic tumour
PERIPHERAL NERVE SHEATH TUMORS	Schwannoma NOS Neurofibroma NOS Granular cell tumour NOS Granular cell tumour, malignant
SMOOTH MUSCLE TUMORS	Leiomyoma NOS Cutaneous leiomyoma Leiomyoma of the nipple and areola Leiomyosarcoma
ADIPOCYTIC TUMORS	Lipoma NOS Angiolipoma NOS Liposarcoma NOS

OTHER MESENCHYMAL TUMORS AND TUMOR – LIKE CONDITIONS	Pseudoangiomatous stromal hyperplasia
FIBROEPITHELIAL TUMOURS	Fibroadenoma NOS Phyllodes tumour NOS Periductal stromal tumour Phyllodes tumour, benign Phyllodes tumour, borderline Phyllodes tumour, malignant Hamartoma
TUMOURS OF THE NIPPLE	Nipple adenoma Syringoma NOS Paget disease of the nipple
MALIGNANT LYMPHOMA	Diffuse large B-cell lymphoma NOS Burkitt lymphoma NOS / Acute leukemia, Burkitt type Endemic Burkitt lymphoma Sporadic Burkitt lymphoma Immunodeficiency associated Burkitt lymphoma Breast implant associated anaplastic large cell lymphoma Mucosa associated lymphoid tissue lymphoma Follicular lymphoma NOS
METASTATIC TUMOURS	
TUMOURS OF THE MALE BREAST	Gynaecomastia Carcinoma Invasive carcinoma In situ carcinoma

INVASIVE DUCTAL CARCINOMA, NOT OTHERWISE SPECIFIED (NOS)

IDC (NOS) type largest group of IBC. It denotes the diverse category of tumours that lack adequate features for classification as a distinct histological type, such as lobular or tubular carcinoma.

Also called as Invasive carcinoma of no specific type (ductal NST), invasive carcinoma not otherwise specified (ductal NOS), IDC. These tumours are a heterogeneous

category of malignancies distinguished by their invasion of adjacent organs and propensity for metastasis. Most of these cancers are formed from the breast parenchymal epithelium particularly the cells of Terminal duct lobular unit (TDLU). They are also described as heterogeneous as they exhibit different morphological, immunohistochemical, prognostic and clinical characteristics.[31,32]

Gross: These tumours exhibit no distinctive macroscopic characteristics. There is a significant variety in size ranging from less than 10 mm to greater than 100 mm. They may possess an uneven, stellate contour or nodular arrangement. The tumour margin is typically moderately or poorly defined and lacks clear delineation. Traditionally, invasive cancer NST is characterized by a solid or hard texture upon palpation and may exhibit a "gritty" sensation when incised with a knife. The sliced surface typically exhibits a grey-white coloration with yellow streaks**.**[24,29]

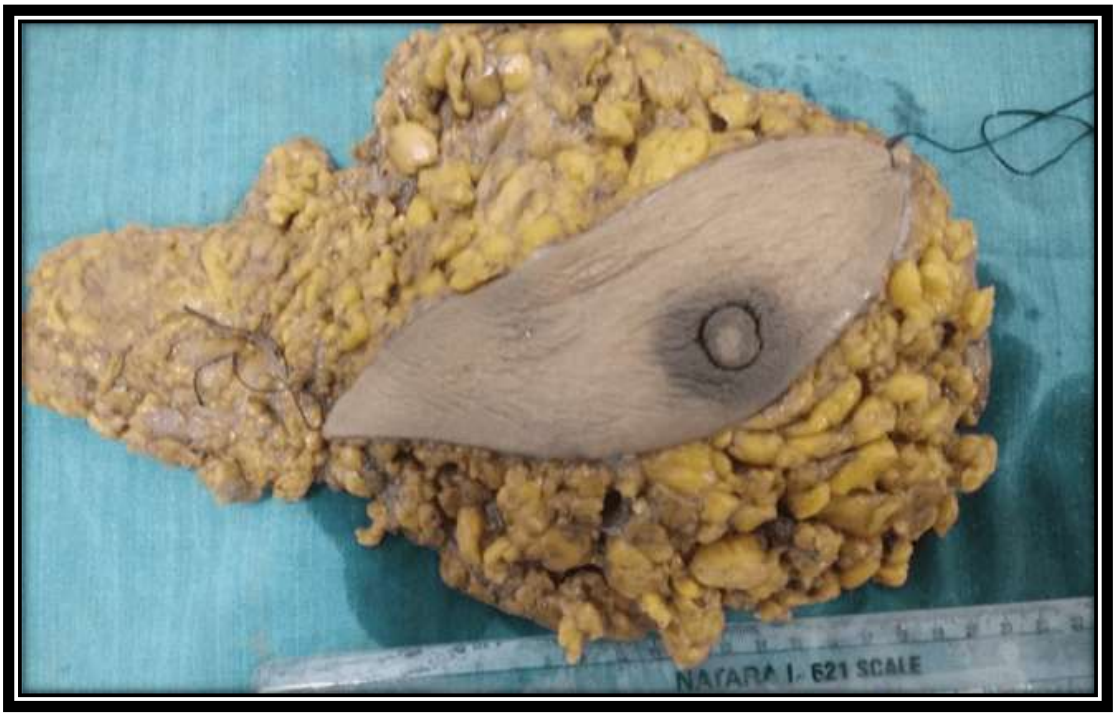


Figure 5 – Gross image of Modified radical mastectomy specimen with axillary clearance of Infiltrating ductal carcinoma breast

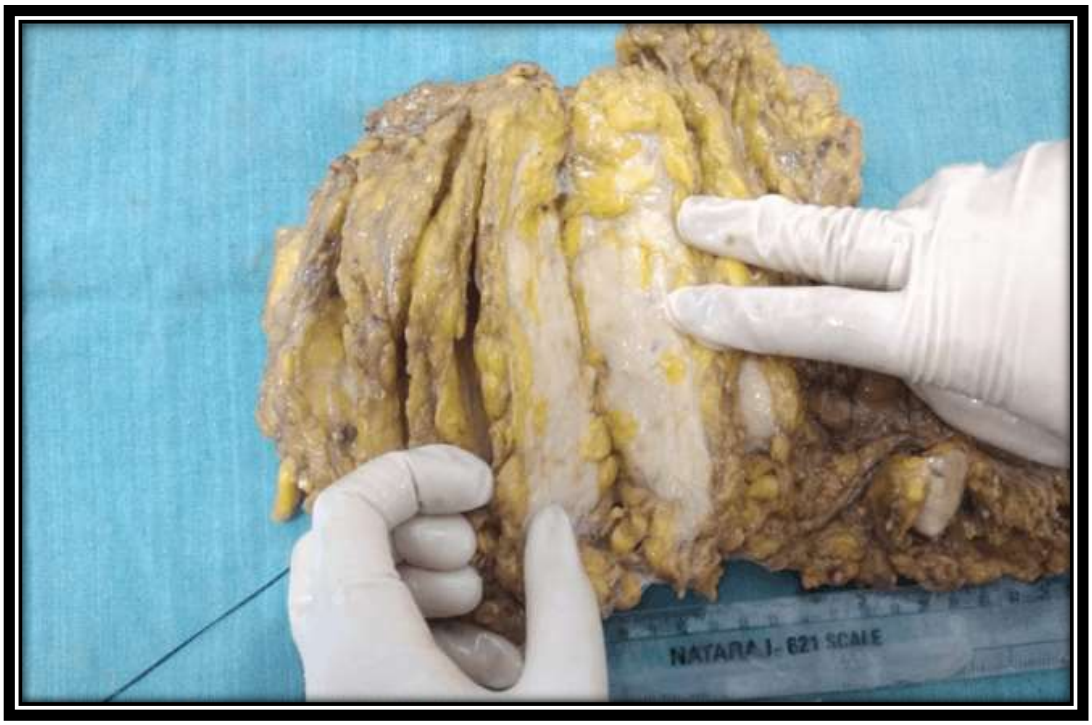


Figure 6– Cut section of the breast showing grey white tumour area

Microscopy- Tumour cells are organized in cords, clusters, and trabecular formations. Few have a robust or syncytial infiltrative pattern with minimal accompanying stroma. The cells exhibit a varied morphology. The cytoplasm is plentiful and eosinophilic. Nuclei can be either normal and homogeneous or very pleomorphic, frequently exhibiting conspicuous, numerous nucleoli. Mitotic activity may be either negligible or widespread. In nearly 80% of instances, foci of concomitant ductal carcinoma in situ (DCIS) will be evident. There may be significant fibroblastic growth, little connective tissue, or pronounced hyalinization. Associated necrosis and periductal elastosis may be observed.

Grading is usually based on Bloom Richardson system of grading. [24,32]

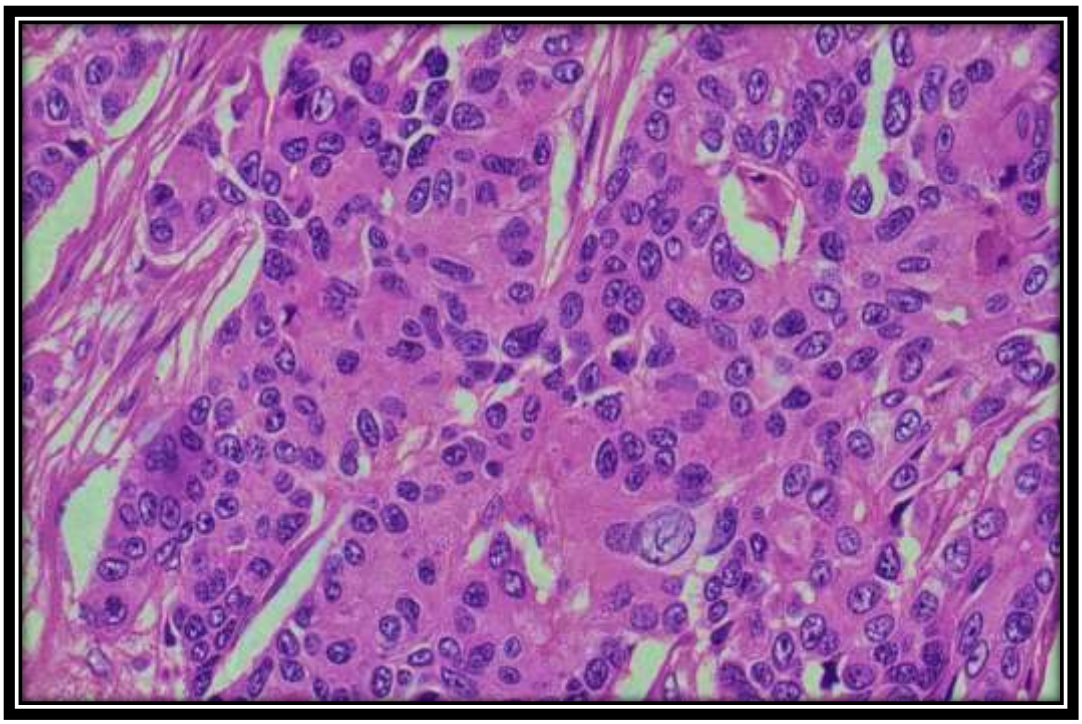


Figure 7: Microphotograph: showing tumour cells are arranged nests and in sheets, individual cells are round to oval with pleomorphic vesicular nuclei having prominent nucleoli. (H&E, 400X)

Lobular- carcinoma:

It constitutes 5-15% of BC. They are usually present with focal in situ lobular carcinomas and gross appearance is often irregular with poorly defined margins. The tumor cells are small to moderately sized cells usually non-cohesive with cells arranged in Indian file pattern.[33]

Tubular carcinoma: Usually comprises 2% of breast cancers and are usually smaller in size (<2 cm). These tumors carry a better prognosis as they are less aggressive, detected due to increased use of mammography. Most lesions tend to be in T1 stage, and 90% of tumor express ER positivity. The most consistent microscopic features is the luminal space lined by a monolayer of epithelial cells.[31,34]

Cribriform Carcinoma: It is the form of well differentiated IDC which has a good prognosis and shows cribriform pattern of growth and is often angulated with well-formed spaces giving a sieve-like appearance. Tumour cells express apical snouts and show moderate degree of nuclear pleomorphism with occasional mitotic figures.[31,32]

Medullary: Usually, account for < 5% of breast malignancies. Due to presence of high amount of lymphoplasmacytic infiltrate in these tumors, they may mimic lymphoepithelial malignancies occurring in other sites.[35,36]

Few distinct histomorphological features are essential for diagnosis of medullary carcinoma. They are-[29,36]

- Symmetrical growth pattern (>75%)
- Absence of glandular structure.
- Diffuse lymphoplasmacytic infiltration.
- Nuclear pleomorphism.
- Complete circumscription.

MUCINOUS CARCINOMA – They are the slow growing tumours of breast consisting of tumour cells suspended or dispersed in pools of mucin. Their size may vary from 1 cm to 20 cm, usually circumscribed bosselated with glistening gelatinous appearance. Rarely cerebral infarction may occur due to mucin embolism and cause death. They carry a fairly good prognosis.[29]

NEUROENDOCRINE TUMOURS – Represent 2-5% of malignant breast lesion usually present in 6th or 7th decade. They are a group of neoplasms exhibiting features of neuroendocrine tumor of lung and gastrointestinal tract. There may be areas of de-

differentiation in infiltrating ductal carcinoma but should show immune reactivity to neuroendocrine markers in >50% of cell population.[29,37]

INVASIVE PAPILLARY CARCINOMA – constitute 1 to 2% of breast malignancies and carry a fairly good prognosis. They are more common in post-menopausal women and have characteristic multiple nodular densities of mammography. Light microscopy shows delicate papillary structures with cells having moderate amount of amphophilic cytoplasm and may also exhibit apical snouting. [31,29]

APOCRINE CARCINOMA – As mammary glands are highly modified sweat glands apocrine carcinoma can also occur in breast with morphological and immunohistology profile of apocrine cells in >90% of cell population. [29]

SECRETORY CARCINOMA – This is usually a low-grade carcinoma that can occur in juvenile and in adults. It is comparatively a rare tumour with tumour cells having intra and extracellular secretory material.[29]

METAPLASTIC CARCINOMA: Metaplastic carcinoma comprises a collection of neoplasms characterized by the development of neoplastic epithelium into squamous cells and/or mesenchymal-like components (spindle, osseous, chondroid, rhabdoid). Comprising around 0.2-1% of all breast cancers, these tumors exhibit an age distribution and clinical characteristics akin to those of ductal carcinoma NOS. This carcinoma comprises a heterogeneous array of tumors. Consequently, a descriptive classification system was implemented**.** [29,38]

Descriptive classification of metaplastic carcinoma[29,38]: -

1) Low-grade adeno-squamous carcinoma

2) Fibromatosis-like metaplastic-carcinoma

3) Spindle cell-carcinoma

4) Squamous cell-carcinoma

5) Mixed metaplastic-carcinoma

6) Metaplastic-carcinoma with mesenchymal-differentiation

pTNM CLASSIFICATION OF BREAST[38]

The AJCC 8th edition has also given staging by pTNM (tumour, nodal status and metastasis) classification, which is the most widely employed system.[38]

TABLE 2 - pT – Primary tumour

pTx	Tumor cannot be assessed
pT0	No evidence of primary tumour
pTis	Ductal carcinoma in situ, Paget‘s disease, encapsulated papillary carcinoma and solid papillary carcinoma
pTis (DCIS)	Ductal carcinoma in situ without invasive carcinoma
pTis(Paget‘s)	Paget disease without invasive carcinoma
pT1mi	Tumor ≤ 1 mm
pT1a	Tumor > 1 mm but ≤ 5 mm
pT1b	Tumor > 5 mm but ≤ 10 mm
pT1c	Tumor > 10 mm but ≤ 20 mm
pT2	Tumor > 20 mm but ≤ 50 mm
pT3	Tumor > 50 mm
pT4a	Extension to chest wall (not including pectoralis muscle)
pT4b	Edema (including peaud'orange), ulceration of skin or ipsilateral satellite skin nodules
pT4c	Both T4a and T4b
pT4d	Inflammatory carcinoma (involves > 1/3 of the breast skin, primarily a clinical diagnosis)

TABLE 3 - Lymph nodes (pN)[38]

pNx	Lymph nodes cannot be assessed
pN0	No regional lymph node metastasis histologically
pN0(-)	No regional lymph node metastasis by histology or immunohistochemistry
pN0(+)	Isolated tumour cells (cluster ≤ 0.2 mm and < 200 cells)
pN1mi	Micrometastasis (tumour deposit > 0.2 mm and ≤ 2.0 mm or ≤ 0.2 mm and > 200 cells)
pN1a	Metastasis in 1 - 3 axillary lymph nodes with at least 1 tumor deposit > 2.0 mm
pN1b	Metastasis in internal mammary sentinel lymph node with tumor deposit > 2.0 mm
pN1c	pN1a and pN1b
pN2a	Metastasis in 4 - 9 axillary lymph nodes with at least 1 tumor deposit > 2.0 mm
pN2b	Metastasis in clinically detected internal mammary nodes with pathologically negative axillary nodes
pN3a	Metastasis in ≥ 10 axillary lymph nodes with at least 1 tumor deposit > 2.0 mm or metastasis to infraclavicular lymph node
pN3b	Positive internal mammary node by imaging with pN1a or pN1b
pN3c	Metastasis in ipsilateral supraclavicular lymph node

TABLE 4 - Distant metastasis (M)

M0	No distant metastasis
pM1	Distant metastasis histologically proven > 0.2 mm

Prefixes

y: preoperative radiotherapy or chemotherapy

r: recurrent tumor stage

TABLE 5 - HISTOPATHOLOGICAL STAGING :[38,39,40,41]

Stage	Tumor	Lymph node	Metastasis
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N0	M0
	T3	N0	M0
Stage IIIA	T0,T1,T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

GRADING OF INVASIVE CARCINOMA OF BREAST:

The histological characteristics of a tumour correlate with its degree of malignancy. [42] In cases of breast cancer, the morphology of the tumour cells can be used to determine the degree of differentiation, which yields valuable prognostic information.[42,43]

Numerous studies have demonstrated a strong correlation between the survival rate of individuals with invasive breast cancer and histological grade. It is an essential part of a pathology report for breast cancer since it is a potent prognostic factor. The Nottingham Prognostic index, also known as the Elston-Ellis variation of the Scarff Bloom-Richardson grading system, is one of the most widely used systems. [38,44]

METHOD OF GRADING:

The grading of invasive carcinomas - breast done based on evaluation criteria include tubule or gland formation, mitotic count, and nuclear pleomorphism. A numerical scoring system guarantees the individual assessment of each factor. Assessment of slide fields representing tumour cell burden is necessary. [38,45,46] Clear central lumina are found in tubules and glandular acini. Scores are assigned using cut-off criteria of 75% and 10% of tumour area with glandular development. Nuclear uniformity in size and shape relative to surrounding normal epithelium determines nuclear pleomorphism. Increased irregularity of nuclear margins and the number of nucleoli is additional features that are useful for scoring pleomorphism. Evaluation of mitosis conducted through the counting of defined mitotic figures. The count of mitotic figures per 10 high-power fields was conducted to assign a score. The peripheral leading edge of the tumour was selected for the assessment of mitotic count. The grade is assigned based on score by adding 3 values. [38]

TABLE 6 – MODIFIED SCARFF-BLOOM-RICHARDSON HISTOLOGICAL GRADING

FEATURES	SCORE
TUBULE / GLAND FORMATION	
>75% of tumour	1
10-75% of tumour	2
<10% of tumour	3
NUCLEAR PLEOMORPHISM	
Small, regular and uniform cells	1
Moderate increase and variability in size	2
Marked variation	3
MITOTIC COUNT / 10 high power fields	
0-5	1
6-10	2
>11	3

Grade 1 (well-differentiated) - 3-5 points

Grade 2 (moderately-differentiated) -6-7 points

Grade 3 (poorly-differentiated) - 8-9 points

EVOLUTION OF PROGNOSTIC INDEX IN BC:

Many of the histological grading schemes used to grade cancer were developed by von Hansemann. He clarified that the likelihood of metastasis increasing with the degree of nuclear atypia, the greater the risk of metastasis occurring.[43]

Greenough created a breast cancer grading system based on the cytological and histological features, it classifies tumours into three histopathological grades. This system includes the proportion of tubule formation, variations in size of both cells and nuclei, the secretory activity of tumour cells, nuclear hyperchromatism and mitotic count.[43]

Patey and Scarff simplified Greenough's technique by considering only three features: tubule formation, nuclear hyperchromatism and variation in the size and shape of the nucleus.[44]

This system of grading was subsequently revised by Bloom and Richardson in 1957. A numerical scoring system was integrated into the existing method, combining nuclear pleomorphism with differentiation measurement and mitotic activity assessment. [43]

In 1957, Emad Rakha and colleagues conducted a comprehensive study involving 2,219 cases. The study observed that the histologic grade, as determined by the Nottingham modification of the Bloom Richardson histological grading system, is a strong predictor of prognosis in patients with invasive breast carcinoma. Therefore, it should be incorporated into breast carcinoma staging systems. [43]

Numerous prognostic factors for breast carcinoma have been identified, yet few of them maintain their independent importance in multivariate analysis. Prognosis is determined by multiple factors, so the best results come from combining significant ones. The

Nottingham prognostic index is a grading method that combines various prognostic factors and is widely used.[43]

NOTTINGHAM PROGNOSTIC INDEX (NPI):

Prognosis assessment of BC is crucial since it helps the physician to assess risk and tailor treatment plans for each patient. Initially described by Galea in 1982, the Nottingham Prognostic Index (NPI) is the sole index that has undergone both intra- and inter-centre prospective validation.[38]

NPI considers factors such as tumour size, histological grade of the tumour and the number of lymph nodes with metastases.

. In a study NPI was used to predict the survival of 80%, 42% and 13% in the 3 groups of breast cancer patients according to the NPI scores. Consequently, it is regarded as a surrogate marker for aggressiveness in BC.[42,43,44]

NPI is calculated by multiplying tumour size (maximum dimension in centimetres) by 0.2, histological grade (according to the Nottingham modification of Bloom Richardson grading system), and lymph node stage (numerical score expressed between 1 and 3).[45,38]

NPI= LN (1-3) + Grade (1-3) + [maximum diameter (cms) x 0.2]

LN is a numerical score assigned to the count of nodes that are positive for malignancy, defined as[38:]

1. 0 positive nodes

2. 1-3 positive nodes

3. ≥4 positive nodes

The prior system utilized a three-tier classification, categorizing cases into good, moderate, and poor prognostic groups according to cut-off values of ≤3.4, 3.4 to 5.4, and >5.4. This system has undergone numerous modifications by researchers over the years, resulting in a classification of four to six tiers, with minor variations in interpretation.[45]

Invasive Breast Cancer Prognostic Factors:

Prognostic factors assist in determining suitable treatment options for breast cancers; however, they do not serve as specific predictors of therapeutic response. Patients exhibiting an excellent prognosis post-surgical removal might not need adjuvant chemotherapy or radiotherapy, given that these interventions can lead to significant morbidity.[46,47] Similarly, patients with a poor prognosis may experience improved survival rates with an aggressive adjuvant approach. Invasive breast cancers exhibit a significantly variable progress. Invasive breast cancers exhibit a significantly variable progress identifying prognostic factors plays a major role.[48,49] Consequently, prognostic and predictive factors in BC have become an important topic of study recent times. [50,51]

The prognosis of IBC depends on several clinical and pathological factors, including:

1) **Age of patient** - After the age of 50, relative survival rates decline. [51,52]

2) **BRCA1 status** – BC patient with BRCA1 mutation carry overall poor prognosis without adjuvant therapy. [53,54]

3) **Pregnancy** – BC diagnosed during pregnancy or lactation are typically malignant tumours with a bad prognosis.[55]

4) **Early diagnosis** – not symptomatic early detection, relative survival rate for people with BC is more.[55]

5) **Presence or absence of invasiveness** – Approximately 50% of patients with IBC presents with local or distant metastasis at the time of diagnosis, so a bad outcome.[53]

6) **Size** - incidence of nodal metastasis and also survival rate is correlated with the tumour size.[54]

7) **Histological type** – few subtypes of IBC including tubular carcinoma, invasive cribriform carcinoma, mucinous carcinoma, ILC, medullary carcinoma been noted to possess favourable prognosis.[54]

8) **Histological grade**

9) **Tumour necrosis** – It has been discovered that lymph node metastases and a lower survival rate are associated with significant tumour necrosis.[55]

10) **Tumour - Infiltrating lymphocytes (TILs)** - The patient's immune response to tumour cells, greater quantity of tumour-infiltrating lymphocytes (TILs) has been correlated with a good prognosis.[55]

11) **Lymph node metastasis** – an increased number of nodes with tumour metastasis has poor prognosis.[55]

12) **Radiation** [51]

IMMUNOHISTOCHEMISTRY (IHC):

IHC is a method that relies on the recognition between antigens and antibodies. This technique is employed to identify specific antigens within cells or tissues through the use of a light microscope. Although the history of IHC extends back to the 1940s, it has only been widely adopted in surgical pathology since the early 1990s.[56]

The enzymatic label (horseradish peroxidase) produced by Avrameas, Nakane, and associates enabled the visualization of the labelled antibody, in conjunction with a chromogenic substrate system, utilizing a light microscope.[56]

Recently, IHC has been utilized for diagnostic reasons, as well as for the identification and confirmation of prognostic and predictive markers.

BIOLOGIC MARKERS IN BREAST:

ESTROGEN RECEPTOR (ER):

This nuclear marker has been shown in both ductal and lobular epithelium, with a greater proportion found in lobules compared to ducts. In premenopausal women, a typical observation is the inverse relationship between estrogen receptor expression and cell proliferation markers. The ER positive cells lack the proliferation marker (anti Ki-67), while the Ki-67 positive cells are typically ER negative. The percentage of cells expressing ER shows a gradual increase with age, yet remains fairly stable post-menopause.[57]

Two forms of estrogen receptors, ER α and ER β, are expressed in normal breast tissue. The expression levels of ER α fluctuate throughout the menstrual cycle, while ER β remains stable without such variations. Myoepithelial cells exhibit no immunoreactivity for ER α, while expressing ER β. Elevated levels of ER β were found to confer protection against neoplastic progression in breast tissue.[57]

PROGESTERONE RECEPTOR (PR):

The progesterone receptor is referred to as NR3C3, which stands for nuclear receptor subfamily 3, group C, member 3. This is a nuclear protein activated by the steroid hormone progesterone. This nuclear marker is present in both lobular and ductal epithelial cells. The expression of PR remains consistent throughout the menstrual cycle. [56,57]

PROTOCOL FOR REPORTING ER AND PR IHC:

ASCO and CAP have provided guidelines for the reporting of results from immunohistochemical assays for estrogen receptor (ER) and progesterone receptor (PR). Numerous studies indicate that cases exhibiting elevated hormone receptor levels are correlated with a favourable response to hormonal therapy. The expression of receptors in as few as 1% of tumour cells has been linked to clinical response. Based on the analysis of these results, the guidelines advocate for the classification of all cases exhibiting a minimum of 1% positive cells as receptor positive.[58,59,60]

SCORING SYSTEM FOR ER AND PR EVALUATION[29,30]:

Two widely utilized scoring systems, the Allred and H scores, are employed to quantify the immunoreactivity of tumor cells for estrogen and progesterone receptors. The Allred score quantifies the expression of estrogen receptors (ER) and progesterone receptors (PR) in tumor cells. The assessment involves both the percentage of positive cells and the staining intensity in the predominant carcinoma. The two scores are summed to yield a final score. (Allred Score)

TABLE 7 – ALLRED SCORING: PROPORTION SCORE[29,30]

Proportion Score (PS)	% Positive Cells
0	0
1	<1%
2	1-10%
3	11-33%
4	34-66%
5	>67%

TABLE 8 – ALLRED SCORING: INTENSITY SCORE[29,30]

Intensity score (IS)	Intensity of positivity
0	None
1	Weak
2	Intermediate
3	Strong

The Intensity and Proportionate scores are added for a total score.[29,30]

HER-2/neu:

HER2/neu is a product of the proto-oncogene, also known as c-erB-2. The increased levels and overproduction of this protein in breast carcinoma correlate with unfavourable survival outcomes.[59,60]

The primary significance lies in its established role as a predictor of response to targeted therapy directed at this transmembrane protein.[53,60,61]

The correlation between HER2/neu and breast carcinoma was initially identified by Vijver et al. in 1988.[62] Azizunnisa et al. conducted a study in 2008 involving 150 cases, concluding that 24.7% of breast cancer cases exhibit HER2/neu overexpression, which is associated with an increase in tumor size and grade.[63]

The American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) provide guidelines for HER2 testing, including reporting intratumoral heterogeneity of HER2 gene amplification when present.[64]

TABLE 9- REPORTING RESULTS OF HER2 NEU TESTING BY IHC:[38]

IHC	RESULTS CRITERIA
Negative (Score 0)	No immunoreactivity or immunoreactivity in ≤10% of tumour cells.
Negative (Score 1)	Faint weak immunoreactivity in >10% of tumour cells but only a portion of the membrane is positive.
Equivocal (Score 2)	Weak to moderate complete membrane immunoreactivity in >10% of tumour cells or circumferential intense membrane staining in ≤30% of cells.
Positive (Score 3)	More than 30% of the tumour cells must show circumferential intense and uniform membrane staining. A homogeneous (chicken wire) pattern should be present.

PROLIFERATION INDEX:

Antigen Ki-67 is a cellular marker associated with proliferation, encoded by the MKI-67 gene. The protein is detectable using the monoclonal antibody Ki-67 (MIB1). This nuclear protein is crucial for cellular proliferation and is linked to ribosomal RNA transcription. Ki-67 antigen is expressed throughout all active phases of the cell cycle, including G1, S, G2, and mitosis, while it is absent in quiescent cells (G0). Ki-67 is identified as a reliable marker for evaluating the growth fraction of a specific cell population. The proportion of tumour cells exhibiting positivity for KI-67 frequently correlates with the clinical progression of breast carcinoma. [65,66]

RECEPTOR STATUS:

Immunohistochemistry (IHC) is employed to evaluate receptor status in breast carcinoma, specifically assessing the presence of estrogen receptors, progesterone receptors and Her2 receptors. This assessment is crucial for determining the appropriate application of targeted therapy, which has emerged as a highly effective adjuvant treatment for breast carcinoma, contributing to improved outcomes. Evaluation of receptor status facilitates the categorization of breast carcinoma into various molecular subtypes. The following are the clinicopathological definitions of invasive breast carcinoma subtypes as established by the thirteenth St. Gallen international breast cancer conference in 2013.[67]

MOLECULAR CLASSIFICATION OF BREAST CARCINOMA[29]

1. Luminal A-like

- ER – positive
- PR – positive
- Her2 – negative
- Ki 67 (proliferation index) - low (<15%)
- Expression of luminal (low-molecular-weight) cytokeratins, and high expression of hormone receptors and associated genes.
- ~ 60% of invasive breast cancers.

2. Luminal B-like (HER2-negative)

- ER – positive
- Her2 – negative
- Expression of luminal (low-molecular-weight) cytokeratins and moderate to weak expression of progesterone receptor and associated genes.
- At least one of the following

- Ki 67 (proliferation index) – high (>15%)
- PR – low or negative

- ~10% of invasive breast cancers

3. Luminal B-like (HER2-positive)

- ER – positive
- Her2 – amplified or overexpressed
- Ki 67 (proliferation index) -any
- PR – any

4. HER2 ENRICHED

- Her2 – amplified or overexpressed
- ER – absent
- PR – absent
- ~15% of invasive breast cancers
- High proliferation rate TP53 mutation common
- May be high grade and node positive

5. Basal like or Triple negative breast carcinoma

- ER – absent
- PR – absent
- Her2-negative High expression of basal epithelial genes, basal cytokeratins
- ~15% of invasive breast cancers
- High proliferation rate TP53mutation common
- BRCA1 dysfunction (germline, sporadic)

These molecular classes play an important role in clinical evaluation because each subtype have different prognosis and different response to specific therapies.[67]

- Cancers with a positive ER/PR status have a better prognosis than those with a negative ER/PR status, and vice versa.[66]
- The Her2/neu receptor, a prognostic and predictive marker in breast cancer, is overexpressed in around 10-20% of invasive cases.[68,69,70]
- Her2 receptor amplification correlates with unfavourable outcomes.[68,69,70]

Triple Negative Breast Carcinoma

Triple-negative breast tumours (TNBCs) are classified as aggressive variants of breast cancer, with distinct metastatic patterns and unfavourable prognosis.[71] They are caused by the downregulation of the human growth factor receptor 2 and the progesterone and estrogen receptors.[72] According to the guidelines set forth by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP), triple-negative breast cancers (TNBCs) are typically characterized by progesterone and estrogen receptor expression at ≤1% and human epidermal growth factor receptor 2 (HER2) expression between 0 and 1+, as determined by immunohistochemistry.[73] Triple-negative breast cancers (TNBCs) comprise four transcriptional subtypes: two basal subtypes, designated BL1 and BL2, a mesenchymal subtype (M), and a luminal androgen receptor subtype.[74] Additionally, TNBC can be classified into six distinct subgroups according to their molecular heterogeneity: immunomodulatory, luminal androgen receptor expression, mesenchymal stem-like, mesenchymal-like, basal-like, and unstable.[75] Triple-negative breast cancers constitute 24% of newly diagnosed breast cancer cases, with a consistent rise in their occurrence documented.[76]

Epidemiology of Triple-Negative Breast Cancer

TNBC constitutes 15–25% of all breast cancer cases.[77] In the US, triple-negative breast cancer (TNBC) accounts for 12% of breast cancer cases, exhibiting a 5-year survival rate of 8–16%.[78] African American and Hispanic women are identified as being at elevated risk for TNBC, with African Americans exhibiting a poorer outcome relative to other ethnicities.[79]

POTENTIAL RISK FACTORS OF TNBC:

Age: Luminal A subtype cancer is more common in persons over 70 years of age, while TNBC is typically diagnosed in those younger than 40 years.[80]

Genetic Mutations: TNBC has been reported to be substantially related with mutations in genes including BRCA1 and BRCA2.[81] The incidence of TNBC are also linked to mutations in TP53, CDH1, PTEN, and STK1.[82,83]

Race/Ethnicity: White non-Hispanic women exhibit a significant prevalence of triple-negative breast cancer (TNBC). [84] Higher mortality rate is seen Black women.[85]

The complexities of TNBC Metastasis

Triple-negative breast cancer (TNBC) represents one of the most aggressive subtypes of cancer, frequently linked to unfavourable patient prognoses due to the emergence of metastases in secondary organs such as the brain, bones, and lungs.[86] The metastatic dissemination of cancer is a multifaceted and inadequately understood phenomenon, encompassing several stages, including angiogenesis, the acquisition of invasive characteristics via epigenetic and genetic alterations, invasion through the basement membrane, extravasation of specific cancer cells to remote tissues, and interactions between tumour and stroma.[87,88] The proliferation of metastatic cells with in a foreign tissue milieu is regarded as the critical barrier in BC metastasis; at this phase, BC cells are challenging to identify and chemotherapeutic resistance attributable to their restricted proliferation.[89,90] The successful reactivation from dormancy results from the continued evolution of surviving disseminated tumour cells through the accumulation of molecular alterations and favourable interactions with the tumour microenvironment.[89]

Subcategories of TNBC:

The subtypes of triple-negative breast cancers (TNBCs) generally exhibit resemblance to basal-like breast cancer (BLBC) in terms of overlapping gene expression profiles. [77] Six subtypes of TNBC were identified based on gene expression profiles, each exhibiting distinct gene expression features and ontologies: basal-like 1 (BL-1), basal-like 2 (BL-2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR)[91,92] (Figure 8). However, the majority of TNBC (80%) have markers associated with basal-like tumours, such as basal cytokeratin, vimentin, EGFR, and mutant BRCA1/2.[93] The genetic differences among these TNBC subtypes indicate the necessity for personalized treatment instead of a general approach.[94]

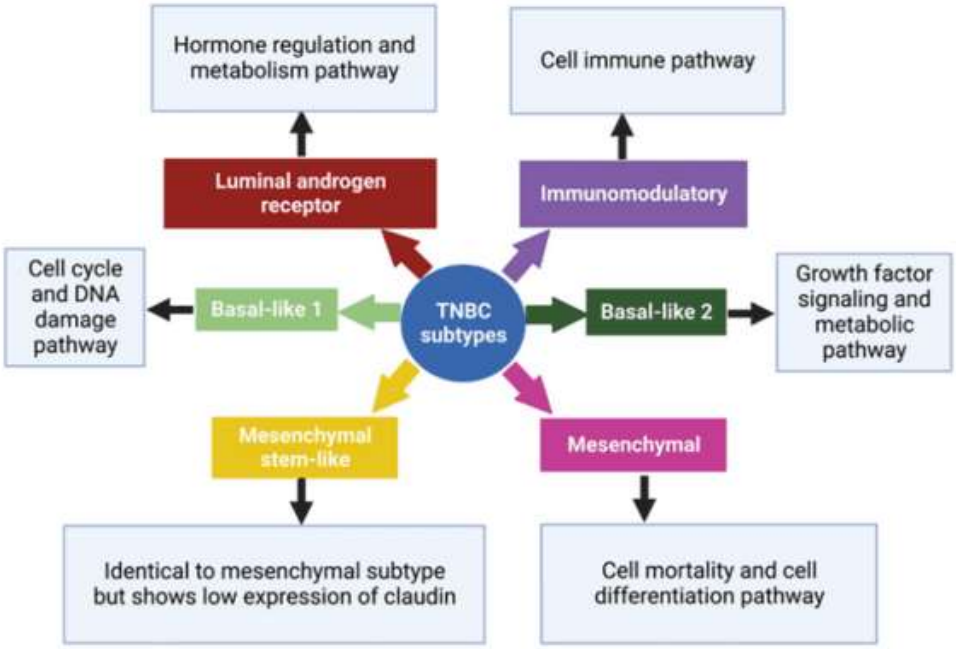


Figure 8: Subtypes of TNBC together with their distinctive paths. Six subtypes of TNBC have been identified according to distinct gene expression profiles and ontologies.[91]

SIGNALING PATHWAYS[95]

1. Notch Signalling Pathway (Fig:9)
2. Wnt/β-Catenin Pathway
3. TGF-β Signalling Pathway
4. CSPG4Protein Signalling Pathway
5. Hedgehog Signalling Pathway
6. PI3K/AKT/mTOR Pathway
7. Epidermal Growth Factor Receptor (Fig:10)

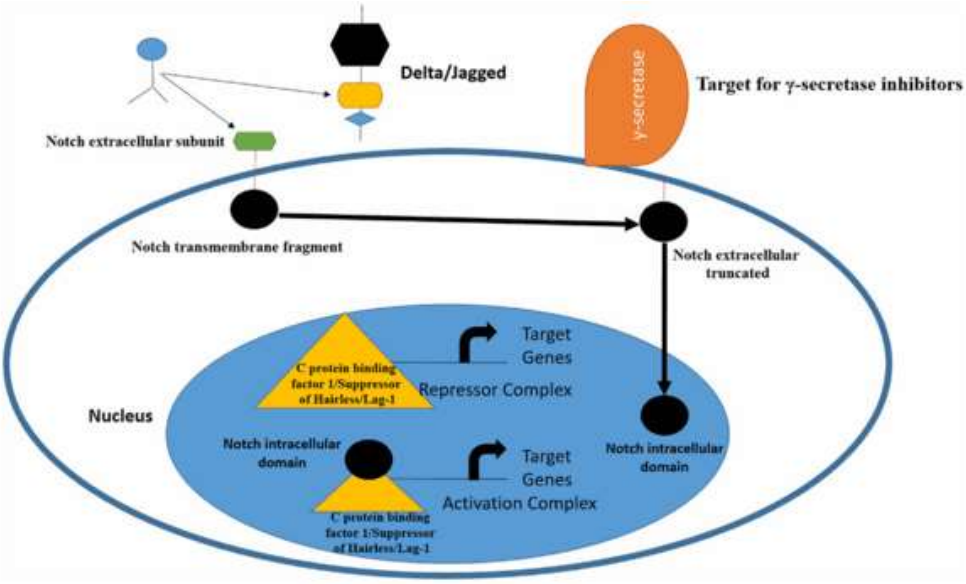


Figure 9: Schematic depiction between Notch receptor stimulation and potential therapeutic strategies. The pathway starts through ligand binding to the Notch receptor, subsequently leading to proteolytic cleavage by proteases. This process releases the Notch intracellular domain, which then translocate to the nucleus to bind with C protein-binding factor1/Suppressor of Hairless/Lag-1, thereby facilitating the conversion of the complex from a repressor to an activator of Notch genes. From an

inhibition perspective, γ-secretase inhibitors and monoclonal antibodies can obstruct Notch ligands and receptors.[96,97]

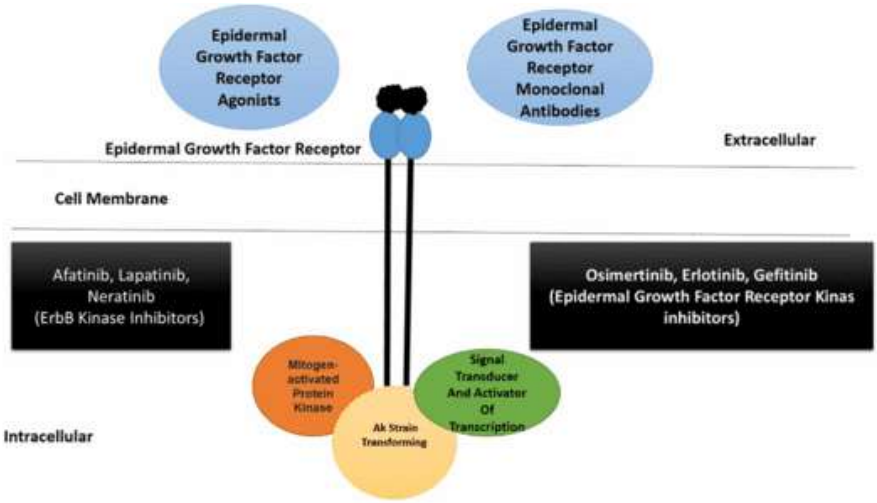


Figure 10: A schematic representation of the EGFR signalling pathway, including its activators and inhibitors. The pathway belongs to the ErbB superfamily. The EGFR can bind various ligands at its extracellular surface, leading to downstream activation of signalling events. Therapeutics, including monoclonal antibodies and diverse kinase inhibitors, can obstruct the ligand's binding to the receptor. The kinase inhibitors can inhibit the function of other ErbB receptors as well as polyadenosine diphosphate-ribose polymerase inhibitors.[97,98]

Immunosuppressive Immune Cells within the Tumour Microenvironment (TME) of TNBC:

The TME encompasses surrounding blood vessels, fibroblasts, immune cells, signalling molecules, and the extracellular matrix around the tumour.[99] Tumour Infiltrating Lymphocytes (TILs) generate an intrinsic antitumor immune response that inhibits the proliferation of tumours and enhances the survival rate of patients with TNBC.[100,101] Tumour-associated macrophages play a significant immunosuppressive role through the secretion of inhibitory cytokines, the promotion of regulatory T cell infiltration, and

the reduction of reactive oxygen species.[101] Cancer-associated fibroblasts reduce anti-tumour immunity, enhance tumour cell proliferation and invasion, and alter the extracellular matrix.[101] Tumour-associated neutrophils facilitate the lysis of tumour cells and promote anticancer activity.[102] (Figure 11)

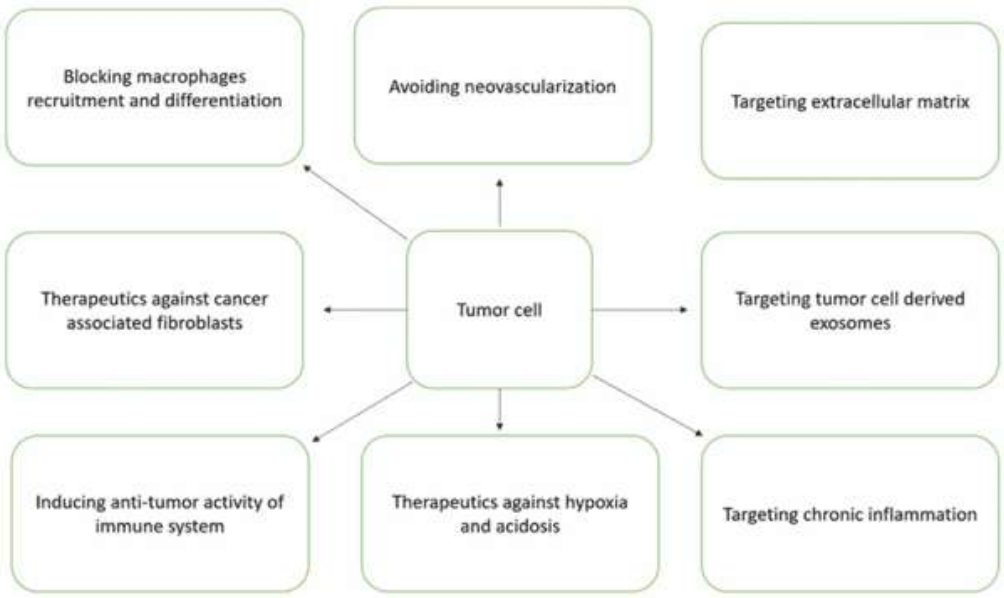


Figure 11: Targeting Tumour Microenvironment for TNBC Therapy[102,103]

LAMININ 332:

- Also known as Laminin 5.
- Laminin is a glycoprotein that plays several roles in cancer progression, cell proliferation, invasion, metastasis, and epithelial-mesenchymal transition (EMT) are included. [104]
- Laminin is a heterotrimeric glycoprotein that performs a variety of functions both during embryonic development and in mature tissues.[8] During embryonic development, this extracellular matrix protein mediates cell attachment, migration, and tissue organization.[9]

- It also aids in cellular differentiation and survival, as well as the growth of embryonic stem cells.[10]
- Laminin 332 is a component of the epithelial and vascular basement membranes in mature tissue, where it aids in the maintenance of cell adhesion and cohesion. Both epithelial and stromal cells secrete Laminin 332, and it binds to integrin receptors on cell surfaces.[9]
- Laminin 332 expression has been linked to tumour progression in addition to its physiological roles. During invasion, cancer cells express laminin on their cell membranes to avoid anoikis(apoptosis caused by cell detachment from the basement membrane).
- Laminin expression has been linked to carcinogenesis hallmarks such as cell proliferation, invasion, metastasis, and the epithelial-mesenchymal transition (EMT). Laminin 332 is located in the cytoplasm of tumour cells and at the interface between the tumor and the surrounding stroma. Basal cell carcinoma, advanced breast cancer, and prostatic cancer exhibit elevated laminin 332 expression levels.[9]
- Triple negative breast cancer exhibits a higher propensity for distant metastasis and recurrence post-treatment. Immunohistochemical studies indicate that approximately 70% of triple-negative breast cancers exhibit positive expression of laminin 332 in breast carcinoma.[5]

Tumour cell and extracellular matrix (ECM) interactions:

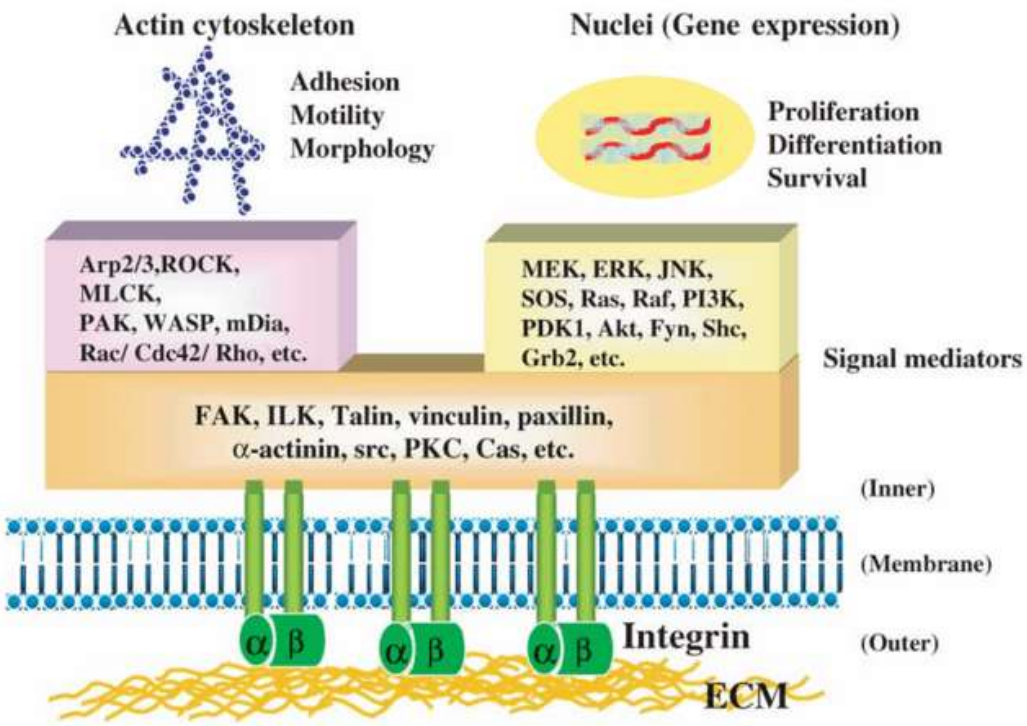


Figure 12: Regulation of cellular activities through integrin signalling.[105]

Integrins, upon binding to extracellular matrix (ECM) molecules, activate intracellular signalling pathways via scaffold proteins, cytoskeletal proteins, protein kinases, and other signalling mediators.

Integrin-mediated signalling, along with receptor tyrosine kinase (RTK) signal transduction, regulates actin organization and gene expression, leading to changes in cellular activities such as adhesion, motility, morphology, proliferation, apoptosis, and differentiation.

The activation of two small GTPases, Rac and Cdc42, in conjunction with phosphatidylinositol-3-kinase (PI3K), is critical for tumour cell motility and invasion**.**

Numerous extracellular matrix (ECM) molecules additionally modulate tumour cell activities through non-integrin receptors. Laminins interact with syndecans, α-

dystroglycan (67-kDa receptor) and integrins.[106] Laminins (LMs) are substantial extracellular glycoproteins that serve as essential constituents of all basement membranes. They participate in various biological activities, such as cellular interactions, self-polymerization, and binding to various extracellular matrix (ECM) proteins.[107,108,109]

All LMs comprise three gene products, α, β, and γ chains, which are gathered into the cross-shaped heterotrimer αβγ. The three chains converge in the endoplasmic reticulum through their C-terminal domains, resulting in a triple-stranded α-helical coiled-coil structure.[110.111] Sixteen LM isoforms, comprising various component compositions derived from five distinct α chains (α1 to α5), three β chains (β1 to β3), and three γ chains (γ1 to γ3), have been found, exhibiting varied expression across different cells and tissues. They are variably detected by cellular receptors.[112] All LM α chains feature a substantial globule at the C-terminal end, comprising five analogous domains, LG1 to LG5, each comprising approximately 200 residues (Fig. 13).

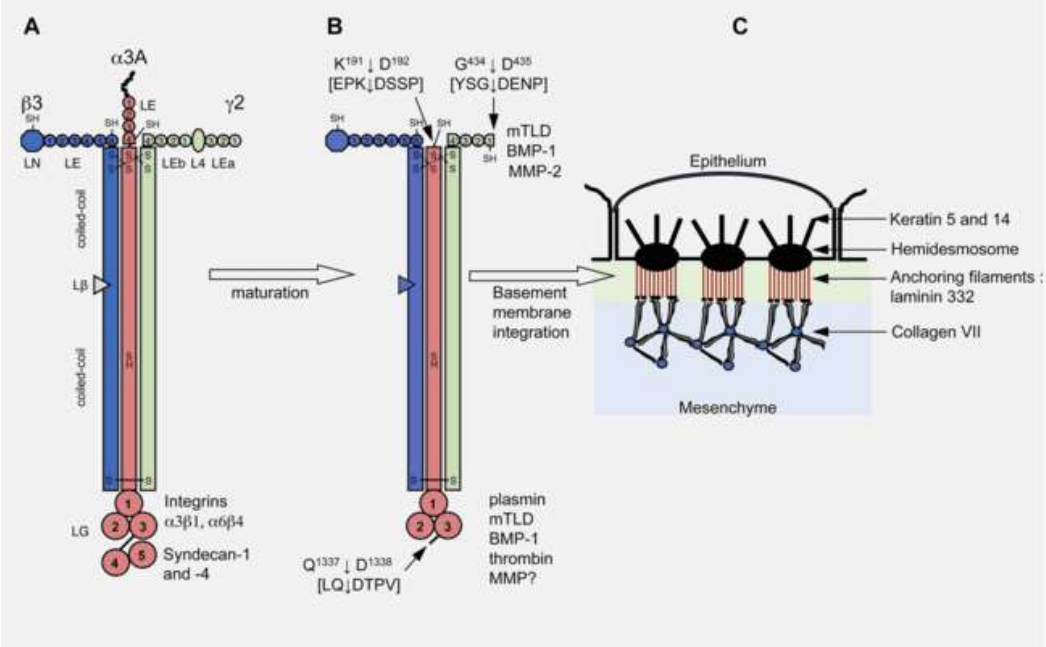


Figure 13: Structure of human LM 332 and its physiological maturation process.[113]

(A) Three subunits comprise LM 332: α3A, β3, and γ2. The domains specified are present in each chain. Five repeating LG domains are located in the significant LG structure at the C-terminal end of the α3 chain. The first three repeats, LG1–3, interact with the α3β1, α6β1, and α6β4 integrins, whereas LG4 and LG5 possess binding sites for syndecan-1 and syndecan-4.

(B) LM 332 is produced as a precursor molecule that undergoes maturation via proteolytic processing at both the N- and C-termini of the α3A chain, in addition to the N-terminus of the γ2 chain. Arrows are employed to indicate the cleavage sites, and the enzymes that are known to be involved are depicted.

(C) A schematic illustration of the anchoring filaments in the dermal–epidermal junction of the skin. Mature LM 332 binds to integrins to connect hemidesmosomes on one side and collagen VII on the other.

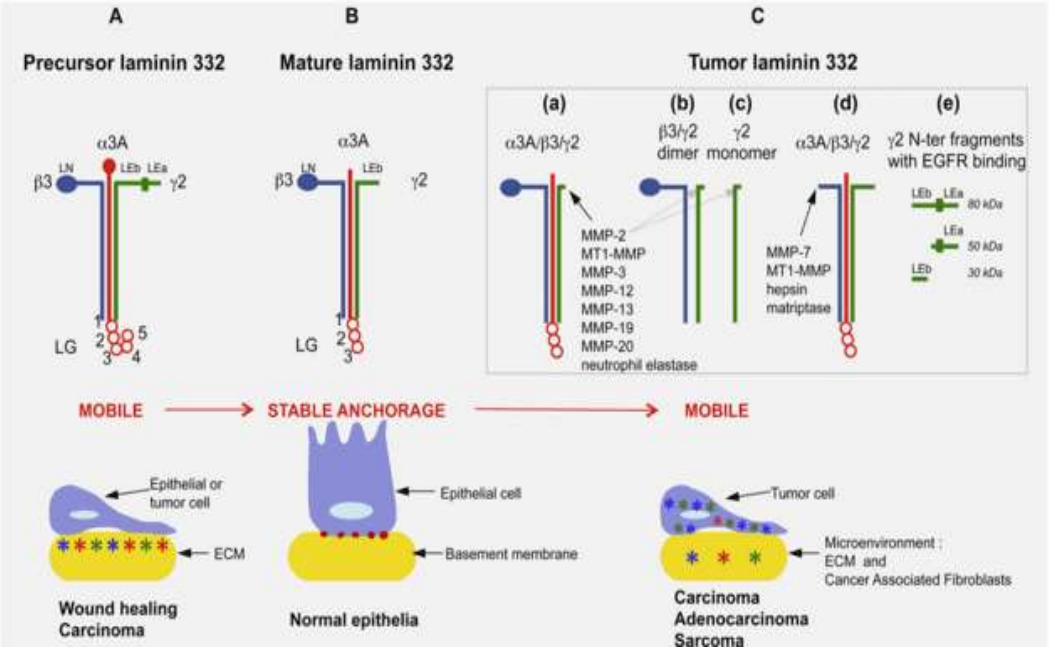


Figure 14: LM 332 processing affects cellular behaviour.[113]

The various molecular forms of LM 332 are linked to distinct biological processes.

(A) LM 332 is present in the extracellular matrix in its precursor form. The high-molecular-weight LM 332 molecule is involved in migratory processes, such as wound healing and cancer.

(B) LM 332, formed during proteolytic maturation of the α3 and γ2 chains, plays a crucial role in anchoring structures and adhesion in resting epithelial cells.

(C) All LM 332 chain cleavages and assembling processes pertinent to cancer biology are illustrated. The γ2 chain in heterotrimeric LM 332 (a), β3/γ2 dimers in tumor laminin 332 (b), or in its monomeric form (c), In several malignancies, the β3 chain of heterotrimeric LM 332 is shortened due to proteolytic cleavage at its amino-terminal end by the specified proteases(d), susceptible to selective cleavage by the designated proteases inside its LEb3 domain, resulting in smaller fragments with pro-tumorigenic characteristics (e).

LM subunits (A, C) are identified in the cytoplasm of tumour cells or inside the microenvironment. The identification of the LM subunits is denoted by stars (α3-red; β3-blue; γ2-green, as illustrated in the LM picture.

Keratinocytes in wound healing: dissolution of stable anchorage

In vivo, elevated expression of LM 332 is a key event in wound epithelialization, with LM 332 being expressed in epidermal keratinocytes within hours after injury, acting as the first basement membrane component deposited into the wound bed. [114,115] The presence of the precursor LM 332 in the migratory keratinocyte matrix suggests that the entire α3 and γ2 chains may be required for this process.[116-119] (Figure 14). The C-terminal LG45 is proposed to contribute to the deposition of LM 332 in the extracellular matrix [120,121] as well as to keratinocyte adhesion and migration.[119,122,123] A variety of peptide sequences have been identified at the C-terminus of the α3 subunit, demonstrating integrin or syndecan-mediated cell adhesion properties and promoting wound re-epithelialization in animal models.[124-128] Syndecan-1 and -4 function as cellular receptors for the LG45 domains.[126,129] Reinforcing the concept that keratinocytes migrate by generating actin-based cellular protrusions[130] or by activating MMP-1 and MMP-9[131]. One of the most important regulators of keratinocyte migration during wound healing is entire γ2 chain [132-134] and is postulated to participate in the integration of LM 332 using its L4 domain during basement membrane construction. [135] The N-terminal region interacts with α2β1 integrin during in vitro keratinocyte migration initiated by transforming growth factor (TGF)-ß1, and this contact is hypothesized to occur at the wound margin during the in vivo skin healing process.[132] Keratinocytes in wounds from early passage cultures express both γ2 chain and the cell cycle inhibitor p16INK4a, resulting in improved directional motility.[133] Further research has demonstrated that hypermotility and growth arrest response of

keratinocytes depends on TGF-ß receptor I-dependent pathway involves both the precursor state of the γ2 chain and serum co-factor.[134]

LM 332 and cancer cells

Several preliminary studies indicated that shared molecular and cellular mechanisms exist in both wounds and cancerous tissue.[136] Unlike wound healing, the process in cancerous tissue is not self-regulating, leading to uncontrolled proliferation of cells, invasion, and metastasis.

The ECM as a dynamic microenvironment player in cancer progression:

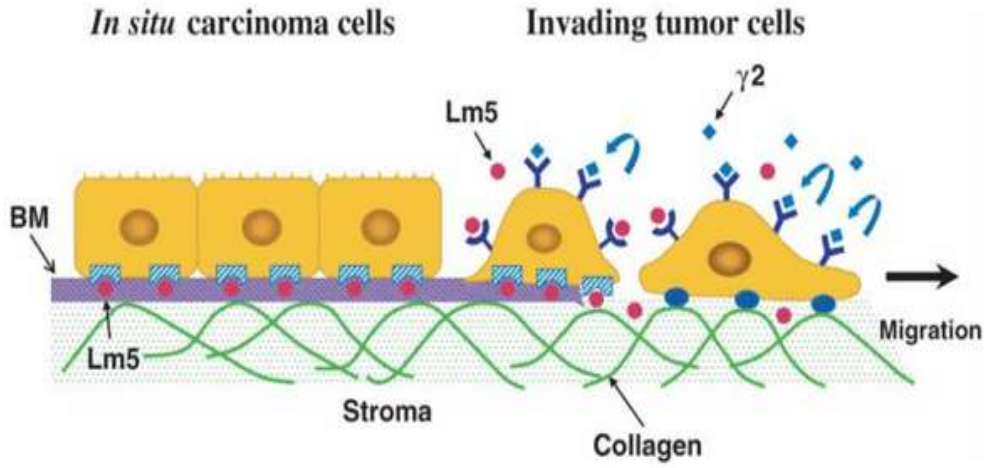


Figure 15: A model for the regulation of tumour cell migration by laminin-5 and its γ2 chain fragments.[137]

In situ carcinoma cells frequently secrete laminin 5 onto the adjacent basement membrane (BM) structures (left side). Laminin-5 (red circles) firmly attaches these cells to the basement membrane (BM) via interacting with integrin α6β4. When the BM structures are not formed or altered, tumour cells might move into the interstitial stroma (right side). Tumour cells near the invasion front exhibit elevated expression of the laminin γ2 chain monomer instead of the laminin-5 trimer. Proteolytic fragments of the

laminin γ2 monomer (blue diamonds) may promote tumour cell invasion by interacting with EGF and other undetected receptors. Laminin-5, when not incorporated into the basement membrane structure, may potentially act as a soluble ligand that promotes tumour cell invasion.

Modifying the fragile equilibrium of ECM signalling is adequate over time to initiate cancer formation and progression.[138] A significant problem in matrix biology is to comprehend its functions in physiological conditions and how the alteration of extracellular matrix dynamics may facilitate cancer formation and progression. A crucial characteristic of epithelial tissues is the specific polarity and architecture of the cells, which are essential for organ formation and function.[139] Extracellular matrix (ECM) is crucial for the formation and preservation of tissue polarity and architecture, properties typically compromised in cancer.

Aberrant ECM dynamics can undermine the basement membrane as a physical barrier and enhance epithelial-mesenchymal transition (EMT), hence facilitating tissue invasion by malignant cells.[140] Overexpression of matrix metalloproteinases (MMPs) can weaken the physical barrier by degrading ECM components. This can disrupt supramolecular networks and release growth factors and bioactive fragments, affecting cellular behavior.[141.142] Supplementary protease-independent invasion of the basement membrane may invade through the physical pressures exerted by the cancer cells themselves.[143] Alterations in extracellular matrix topology may potentially promote cancer cell migration. Collagen fibers exhibit thickening and linearization in malignancies, frequently observed in regions of active tissue invasion and tumour vasculature [144-146], indicating a contributory role in promoting cancer cell invasion.

LM 332 exhibits all of these qualities, since its dysregulated expression in cancer transforms it from an anchor protein that promotes epithelial cell polarity to a protein that facilitates migration and carcinogenesis. LM 322 is situated within the dense fibrotic zone surrounding breast invasive ductal carcinoma, establishing a specialized environment that promotes tumour invasion. It facilitates the formation of focal adhesions in cancer cells and aids in cancer metastasis. The LM γ2 chain exhibits significant expression in invasive mammary, colon, melanoma, and sarcoma cancer cells.

Table 10: Expression of LM332 and its constitutive subunits in cancer[113]

	Tumor type	Intracellular chain retention at the invasive front	Loss of LM 332 in the basement membrane	LM 332 expression in stroma during progression	Indication of metastasis	Serum detection
ADENOCARCINOMA	Breast cancer	γ2 chain	Yes	LM 332 produced by CAFs	High LM 332 in stroma	
	Colorectal cancer	β3/γ2 dimers	Yes	β3/γ2 dimers γ2 monomer Clivage in β3	Decreased β3/γ2 ratio	
	Pancreas ductal adenocarcinoma	α3, β3, γ2 chains	Yes	LM 332 produced by CAFs	γ2 monomer: bad prognosis	γ2 fragments
	Hepatocellular carcinoma	γ2 chain	No LM 332 in the liver	γ2 in the ECM	γ2 chain	γ2 fragments
	Lung adenocarcinoma	γ2 chain (β3?)	Yes		γ2 chain (α3?)	γ2 chain
	Prostate cancer	β3, γ2 chains	Yes	β3 chain variants	Clivage in β3	
SQUAMOUS CELL CARCINOMA	Cutaneous carcinoma	γ2 chain Precursor α3 chain	Yes	High LM 332 Precursor α3 chain	High LM 332 (β3?) High γ2 chain Clivage in γ2	
	Head and neck tumors	α3, γ2 chains		High LM 332	High LM 332 High γ2 chain	γ2 fragments
	Urinary bladder cancer	γ2 chain	Yes		High γ2 chain	γ2 chain and fragments
SARCOMA	Ewing family tumors Spindle cell sarcoma	β3 chain β3 chain				

Breast cancer:

Numerous studies have investigated LM 332 in BC[147-150], indicating that LM 332 facilitates the migration of breast carcinoma cells[151] and is associated with tumour invasiveness. The γ2 chain is seen in the early stages of invasive breast cancer tissues.

[152] While certain authors have reported a loss in LM 332 expression during the course and in advanced breast carcinoma[152-155], others have identified LM 332 in breast stroma and proposed that this localization may provide a microenvironmental signal that

promotes carcinoma invasion in vivo.[149-151] A correlation suggesting a worse prognosis has been observed in a small cohort of 10 patients when tumours co-expressed peritumoral LM332 γ2 chain and β4 integrin.[148] however, no significant prognostic difference between malignancies with and without LM332 was identified. LM332 is widely recognized for its role in enhancing the motility of breast cancer cells via integrins[151] and is linked to breast cancer metastasis[156]. The inhibition of LM 332–specific β3 and γ2 chains through small-interfering RNA may reduce the motility of MDA-MB-231 breast cancer cells while preserving their viability.[154]

Over expression of LM332 has been observed in 70% of triple-negative breast carcinomas.[157] Recent studies of the β3 chain using western blot and immunohistochemistry in a significant patient cohort with extended follow-up have shown that LM332 expression in breast tumour cells is associated with poorer survival outcomes.[158] Consequently, LM332 contributes to the aggressive phenotype of certain breast malignancies and serve as a prognostic indicator for triple-negative breast carcinoma. The malignant transformation of breast epithelial cells is associated with autocrine LM332, which promotes cell survival by activating the α6β4 integrin-RAC-NFkB signalling pathway.[159] The combination of caloric restriction and ionizing radiation promotes tumour regression in triple-negative breast cancer models through a mechanism involving the downregulation of the microRNA miR-17/20a, which targets the LMα3 chain.[160] The findings indicate that the expression of the LMα3 chain in tumour cells reduces their metastatic capability. miR17/20a has been previously identified as a prognostic indicator in oral squamous cell carcinoma due to its tumour-migration-suppressing action.[161] The EGF-like repeats at the N-terminus of LMγ2 interact with CD44 in the metastatic breast cancer cell line MDA-MB-231, facilitating cell migration dependent on CD44 and TGF-β receptor I.[162]

MATERIALS

AND

METHODS

MATERIALS AND METHODS:

Study design: Laboratory - based Cross sectional study.

Study period: 18 Months (May 2023 – October 2024).

Source of data:

Surgical resected specimens and Trucut biopsy samples of TNBC received from Department of Surgery at RL Jalappa Hospital and Research Institute to the Department of Pathology attached to Sri Devaraj Urs Medical college, Tamaka Kolar from January 2019 to October 2024. The data and paraffin blocks were retrieved from the archives of Department of Pathology.

Study tool: Immunohistochemical staining for LAMININ 332 in histopathologically diagnosed cases of Triple negative breast cancer.

Method of collection of the data: All the cases of triple negative breast carcinoma along with clinical details was be collected from Archives of Department of Pathology from January 2019 to October 2024 both prospective and retrospectively.

Inclusion criteria: All cases of histopathologically and immunohistochemically confirmed triple negative (ER, PR, HER2neu negative) breast carcinomas, and the presence of adequate tumour tissue with sufficient connective tissue stroma.

Exclusion criteria: Insufficient tissue, tissue with an inconclusive diagnosis, and cases that had previously undergone surgery, chemotherapy, or radiotherapy was be excluded from the study.

Sample size:

- Sample size estimated by expression of Laminin 332 in Triple negative breast carcinoma was 50 as in study by Rath G *et al* [5] with 95% confidence interval and an absolute error of 15%.
- Formula to be used
- $$\frac{n = Z(1-\alpha)^2 (p)(q)}{d^2}$$

n = sample size

Z (1-α) power at 95% CI = 1.96

P = Prevalence = 53.5%

q = 100-p = 100-53.5 = 46.5

d = Absolute error = 15

$n = 1.96^2 \times 53.5 \times 46.5 / 15^2 = 50$

n = 50

Methodology:

- All the diagnosed triple negative primary carcinoma of breast cases by TRUCUT biopsy and mastectomy were be included.
- Case details were collected from the case files, which include – age, clinical presentation, physical examination findings such as site, size, number of palpable lymph nodes, relevant laboratory and radiological investigations.

- The breast tissue was fixed in 10 % Neutral Buffered Formalin.
- Representative bits were given from the tumour proper along with adjacent tissues.
- The tissue bits were processed as per the protocol.
- Tissue sections were stained with Haematoxylin and Eosin stain subsequently immunostaining was noted.
- The tissue sections were screened and analysed for histomorphological features including Histopathological type, grade and stage of the tumour.
- ER, PR, Her2neu, Ki67 was noted.
- Tissue sections were be subjected to Laminin 332 immunohistochemical staining.

Immuno-Histochemistry staining procedure:

1. De-wax and brought sections to distilled water.
2. Washed briefly in distilled water for 1 – 2 minutes
3. Antigen retrieval was done after 15-20 minutes according to the standardization protocol to the particular antibody in citrate buffer pH 6.0/TRISEDTA pH 9 then cooled for 5-10 minutes.
4. Washed in distilled water; did not let the section dry out. Endogenous Per-oxidase the sectioned in 3% H2O2 for 10 minutes.
5. Washed in tris buffered solution (TBS) pH 7.4 for 2 minutes.
6. The sections were than covered with individual primary antibodies with code number PDM 568 manufactured by Diagnostic Biosystems for 45 to 1 hour based on validation min at room temperature.
7. Washed the slides for two times with TBS for 2 minutes

8. The sections were than covered with secondary antibody (HRP) with code no. KP-5001 manufactured by Diagnostic Biosystems for 30 minutes
9. Washed the slides for two times in TBS for 2 minutes
10. The sections were than covered with Diaminobenzidine tetrahydrochlodide (DAB) chromogen for 5 minutes (R1-1ml, R2-30UL)
11. Washed with distilled water
12. The sections were than covered with hematoxyline for 30 seconds
13. Washed the slides with TBS followed by distilled water 2 times in 2 changes
14. The sections were dehydrated by 3 changes of absolute alcohol & cleared with 2 changes of Xylene for 2 minutes. Mounted with DPX.

Interpretation of Staining[5]

- Internal Positive control used was Skin and Negative control used was breast tissue without antibodies.
- Ten consecutive representative fields were be examined at 10X and 40X, compared to the internal control and scored.
- Internal positive control was taken from the basement membrane of the epithelium.
- The stain distribution and continuity around the basement membrane of malignant epithelial cell nests, as well as within the cytoplasm of the malignant cells was investigated in the tumour section.
- To obtain accurate results, the staining area and intensity both were evaluated.

Table 11: The rates of laminin expression will be measured using a semiquantitative 4-tier system of Intensity Score classification:[5]

Grade	Immunoreactivity Intensity Score	Interpretation
I	0,1+	Absent, weak staining (light yellow)
II	2+	Intermediate or Moderate staining (yellow/brown)
III	3+	strong staining (brown)

Table 12: Interpretation of Proportionate score for Laminin 332 IHC[157,158,165]

Percentage of positive cells	Proportionate Score
<1 %	0
1-5 %	1
5-30 %	2
>30 %	3

Table 13: Calculation of final grade for Laminin 332 IHC Score

Both Laminin332 Intensity IHC score and Proportionate score expressed by Tumour cells were added and final grade is obtained in present study

Final Grade	**Intensity score + Proportionate score**
Grade 1	0-3
Grade 2	4-6
Grade 3	7-9

STATISTICAL ANALYSIS

Statistical analysis

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

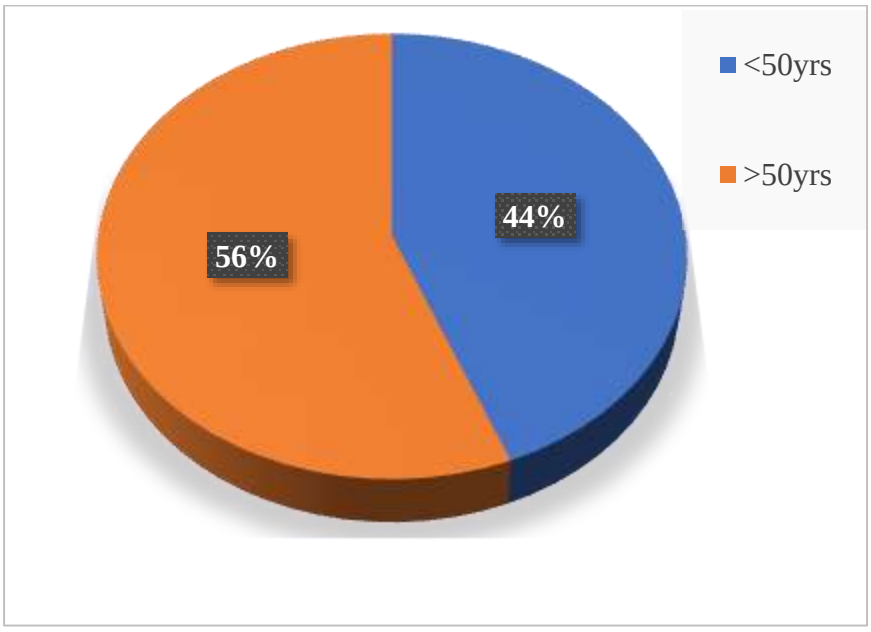
RESULTS

RESULTS

Table 14: - Distribution of subjects according to age group

Age group	Frequency	Percent
<50yrs	22	44.0
>50yrs	28	56.0
Total	50	100.0
Mean age -50.3 years		
Median age -54.5 years		

Chart 1: Pie diagram showing distribution of subjects according to age group

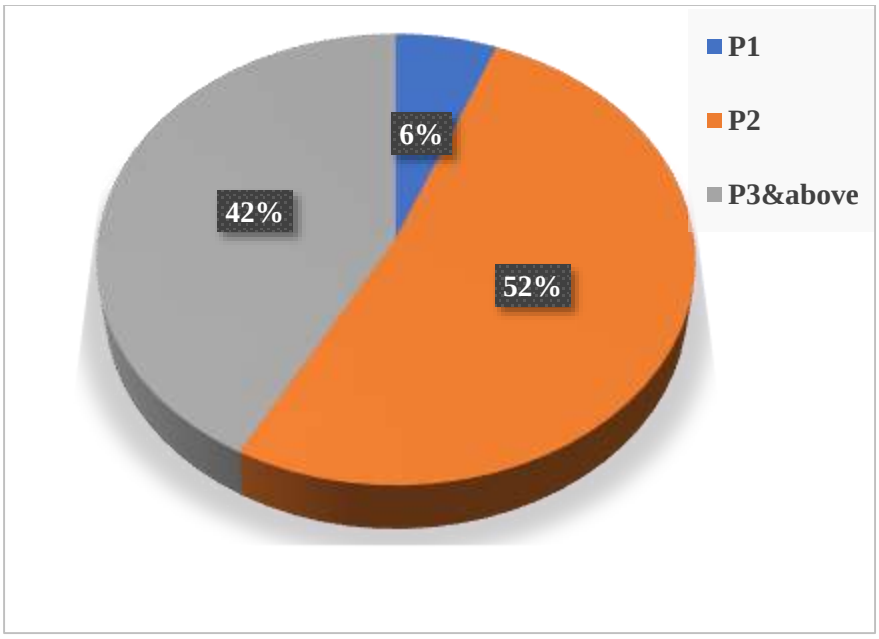


The present study included 50 participants, of whom 22 (44.0%) were younger than 50 years and 28 (56.0%) older than 50 years. A mean of 50.3 years, a median of 54.5 years, suggest that the study group has higher proportion of elderly people (>50 years).

Table 15: - Distribution of subjects according to parity

Parity	Frequency	Percent
P1	3	6.0
P2	26	52.0
P3 & above	21	42.0
TOTAL	50	100

Chart 2: Pie diagram showing distribution of subjects according to parity

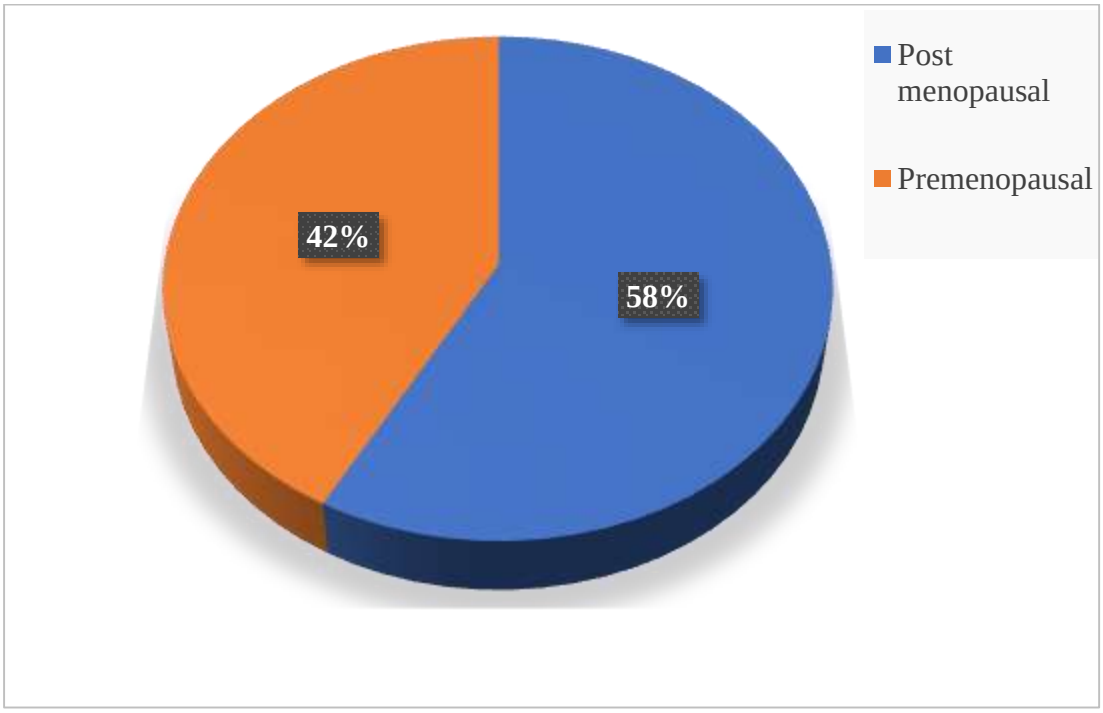


In present study majority of participants were parity of two (P2) 26 (52.0%), 21(42%) were with a parity of three and higher (P3 and above) and 3(6.0%) had parity of one (P1).

Table 16:- Distribution of subjects according to menopausal status

Menopausal status	Frequency	Percent
Post menopausal	29	58.0
Premenopausal	21	42.0
Total	50	100.0

Chart 3:- Pie diagram showing distribution of subjects according to menopausal status

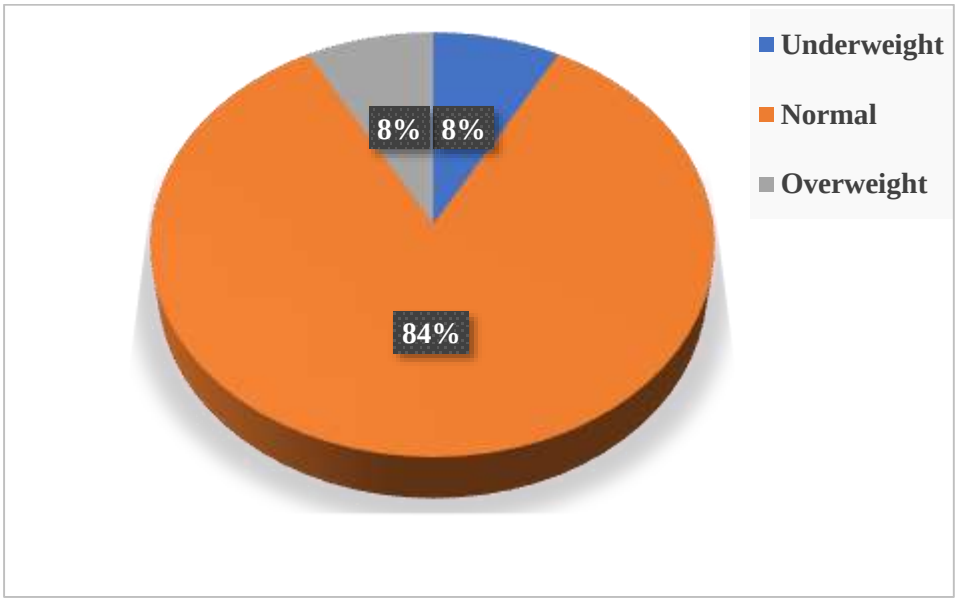


In present study 29 (58%) of study population were postmenopausal and 21(42%) were premenopausal, showing a higher prevalence of postmenopausal women having TNBC.

Table 17:- Distribution of subjects according to Body Mass Index (BMI)

BMI	Frequency	Percent
Underweight	4	8
Normal	42	84
Overweight	4	8
TOTAL	50	100

Chart 4:- Pie diagram showing distribution of subjects according to BMI

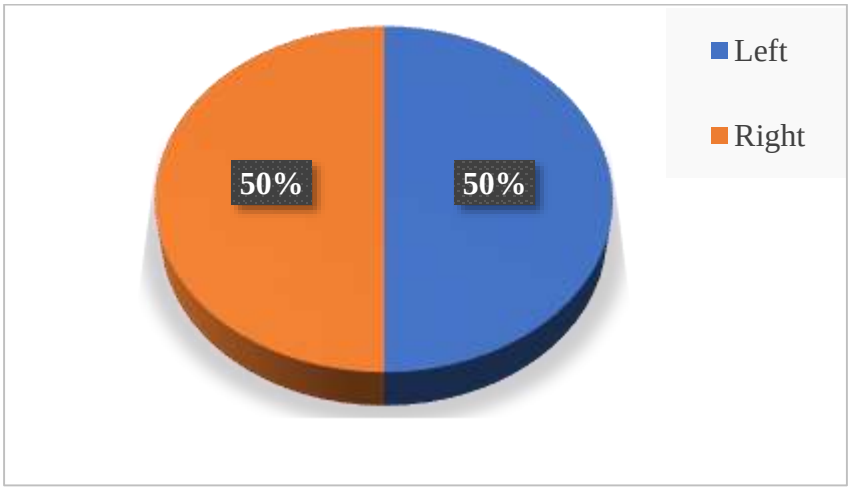


In present study 24(84%) of study population had normal BMI, 4(8%) were underweight and 4(8%) were overweight. Majority of study population had normal BMI.

Table 18: - Distribution of subjects according to laterality of tumour

Laterality	Frequency	Percent
Left	25	50.0
Right	25	50.0
Total	50	100.0

Chart 5: - Pie diagram showing distribution of subjects according to the laterality of the tumour

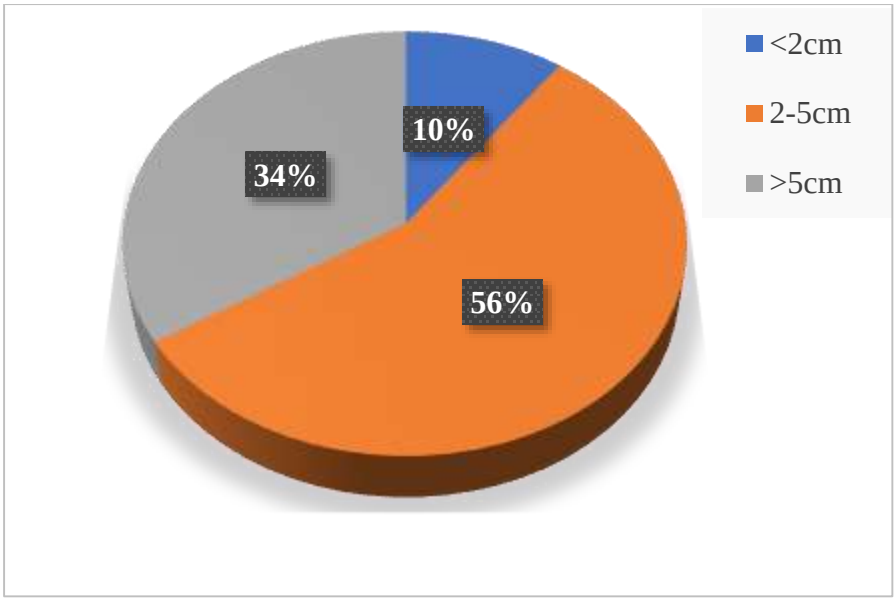


In current study 25(50%) of study population had the tumour in the left breast, and the remaining 25 cases (50%) had the tumour in the right breast, indicating an equal distribution of breast cancer cases between the left and right sides.

Table 19: - Distribution of subjects according to Tumour Size

Tumour Size	Frequency	Percent
<2cm	5	10.0
2-5cm	28	56.0
>5cm	17	34.0

Chart 6: - Pie diagram showing distribution of subjects according to Tumour size

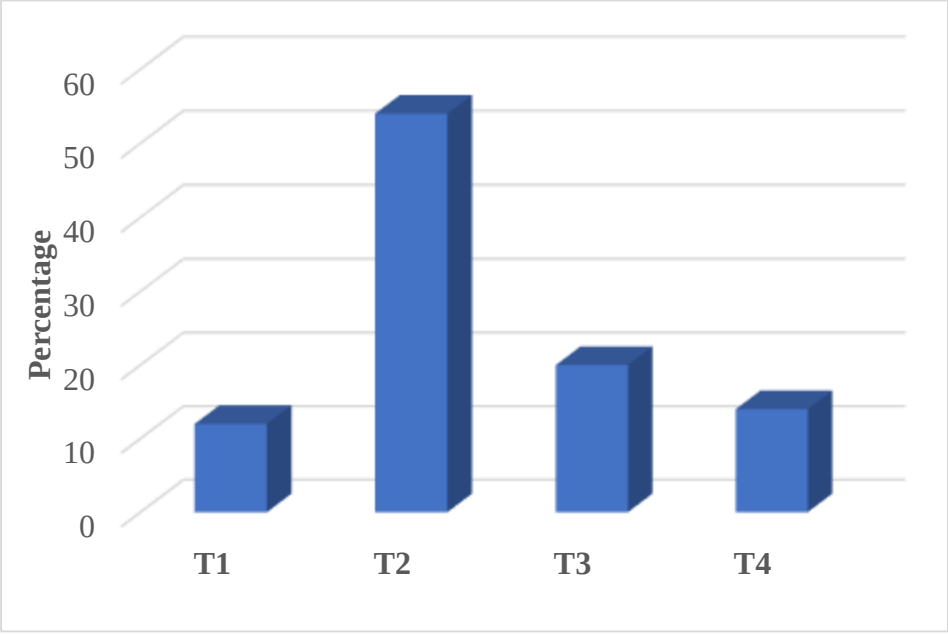


In present study 28(56%) of study population had tumour size 2-5cms, 17(34%) had tumour size of >5cms and 5(10.0%) had tumour size of >2cm. Majority of study population had tumour size of 2–5 cm.

Table 20: - Distribution of subjects according to pT Stage

pT STAGE	Frequency	Percent
pT1	6	12.0
pT2	27	54.0
pT3	10	20.0
pT4	7	14.0
Total	50	100.0

Chart 7:- Bar diagram showing distribution of subjects according to pT stage

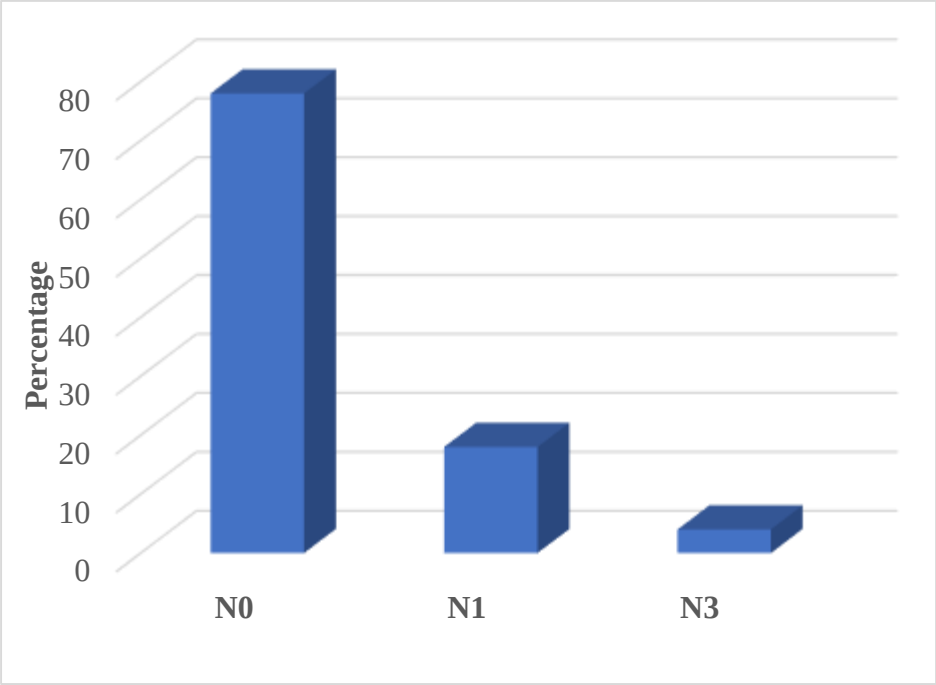


In Present study 27(54%) of study population had pT2 stage, 10(20%) had pT3, 7(14%) had pT4 and 6(12%) had pT1stage. Majority of patients in present study fell under pT2 stage.

Table 21: - Distribution of subjects according to pN Stage

pN Stage	Frequency	Percent
N0	39	78.0
N1	9	18.0
N3	2	4.0
Total	50	100.0

Chart 8: - Bar diagram showing distribution of subjects according to pN Stage

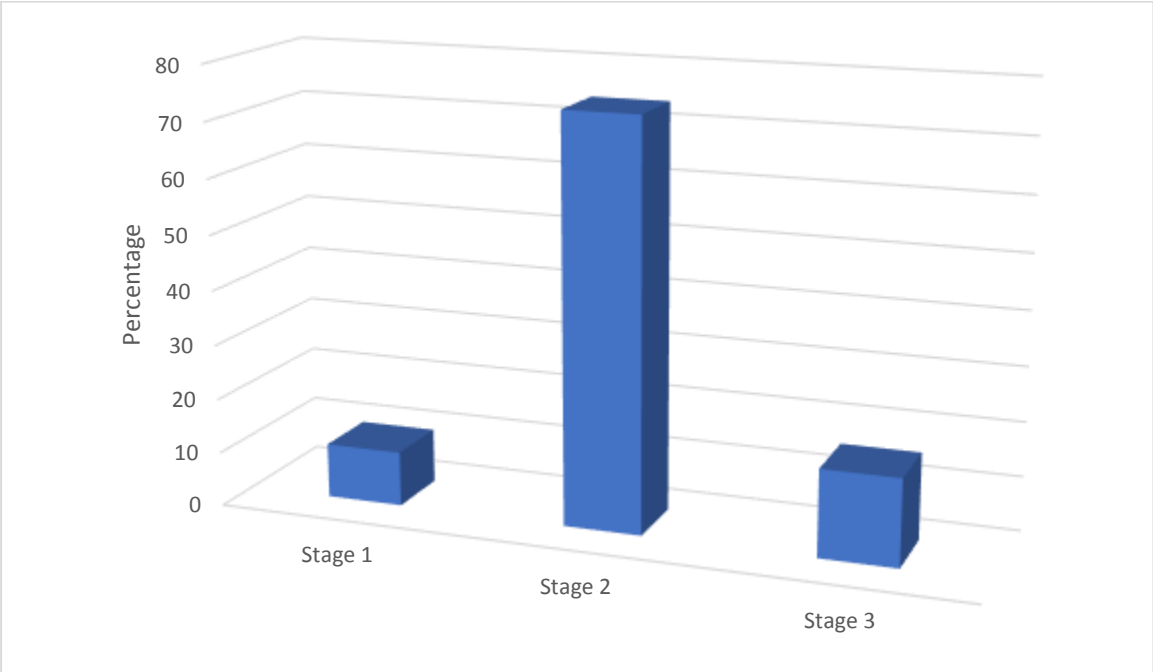


In current study 39(78%) of study population presented with no lymph node involvement (N0), followed by N1 9(18%) and N2 2(4%). Majority of patients presented with no lymph node involvement.

Table 22: - Distribution of subjects according to pTNM Stage

pTNM Stage	Frequency	Percent
Stage 1	5	10.0
Stage 2	37	74.0
Stage 3	8	16.0
Total	50	100.0

Chart 9: - Bar diagram showing the Distribution of subjects according to pTNM staging

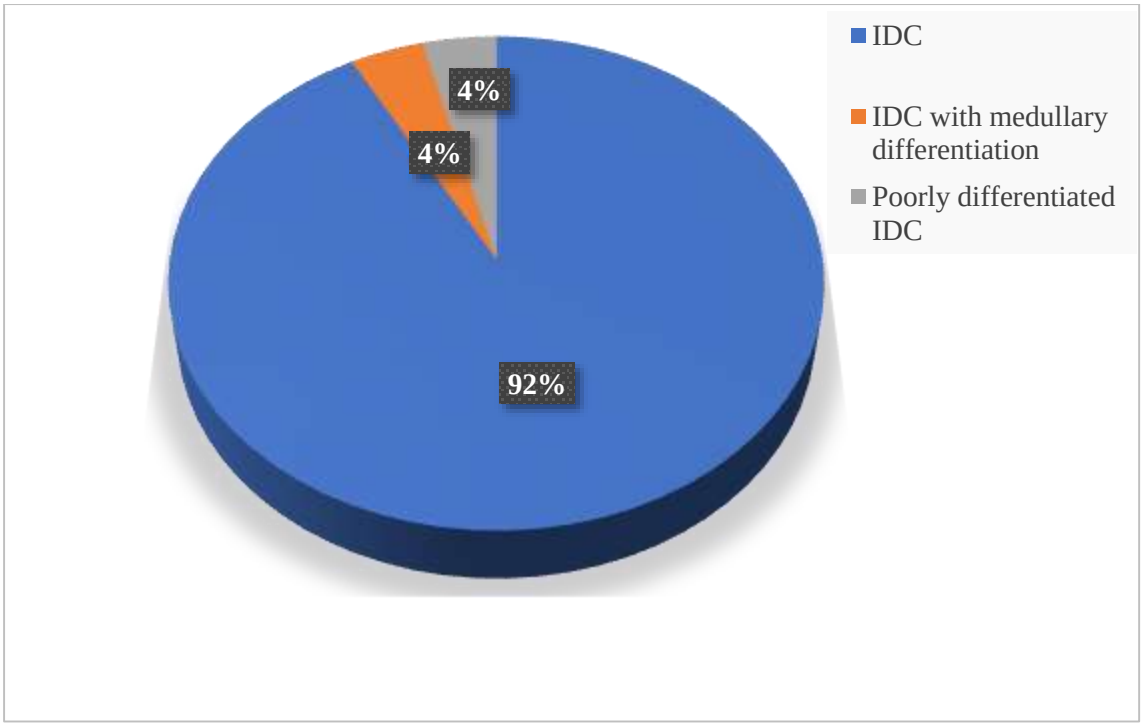


In current study 37(74%) of study population were Stage II, followed by Stage III 8(16%), and only 5(10%) were staged as Stage I. Present study showed majority of study population were stage II.

Table 23: - Distribution of subjects according to histopathological diagnosis

Histopathological Diagnosis	Frequency	Percent
IDC	46	92.0
IDC with medullary differentiation	2	4.0
Poorly differentiated IDC	2	4.0

Chart 10:- Pie diagram showing Distribution of subjects according to histopathological diagnosis

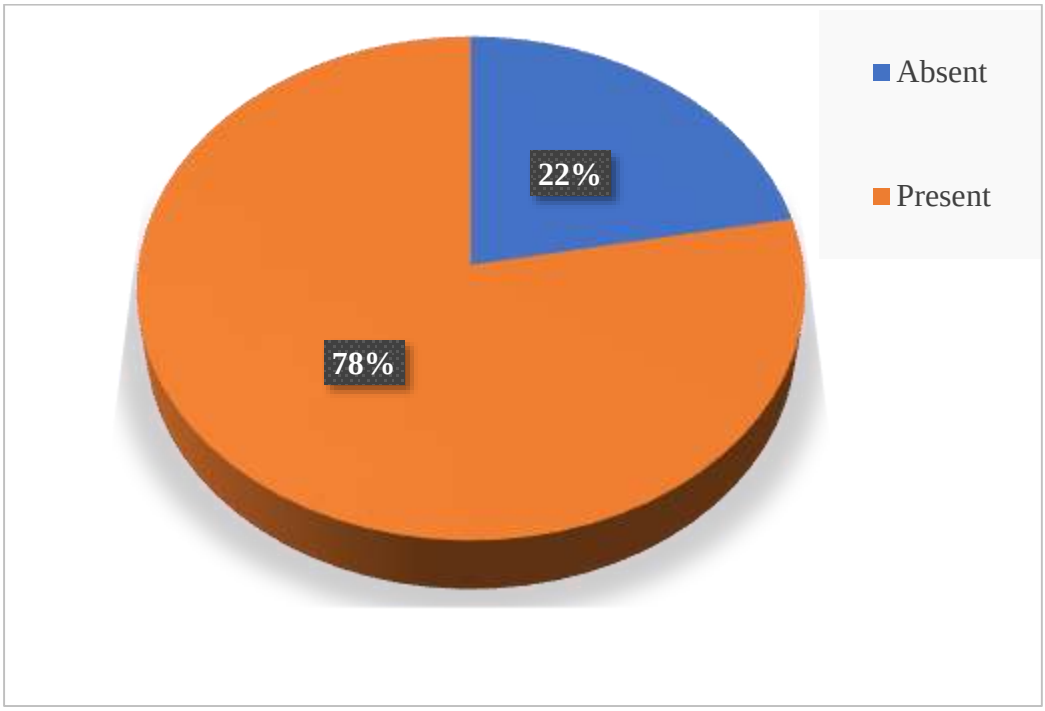


In present study Infiltrating Ductal Carcinoma (IDC) 47(92%) was the most common histological type followed by poorly differentiated IDC 2(4%), Poorly differentiated Infiltrating Ductal Carcinoma with medullary differentiation 2(4%).

Table 24: - Distribution of subjects according to LVI

LVI	Frequency	Percent
Absent	11	22.0
Present	39	78.0
Total	50	100.0

Chart 11: - Pie diagram showing the distribution of subjects according to LVI

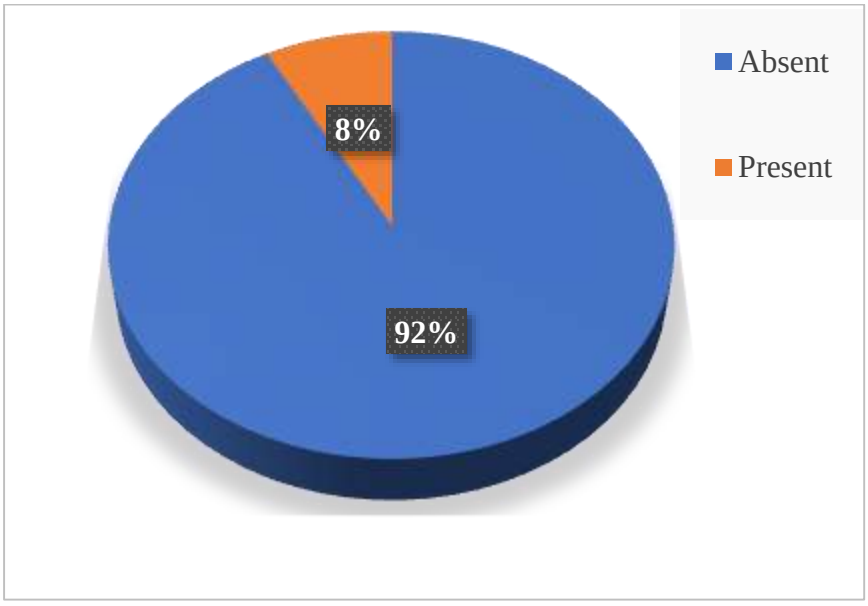


In current study 39(78.0%) of cases had LVI is present and 11(22.0%) of cases LVI did not show LVI , suggested more aggressive tumor behavior.

Table 25:- Distribution of subjects according to PNI

PNI	Frequency	Percent
Absent	46	92
Present	4	8
Total	50	100.0

Chart 12:- Pie diagram showing distribution of subjects according to PNI

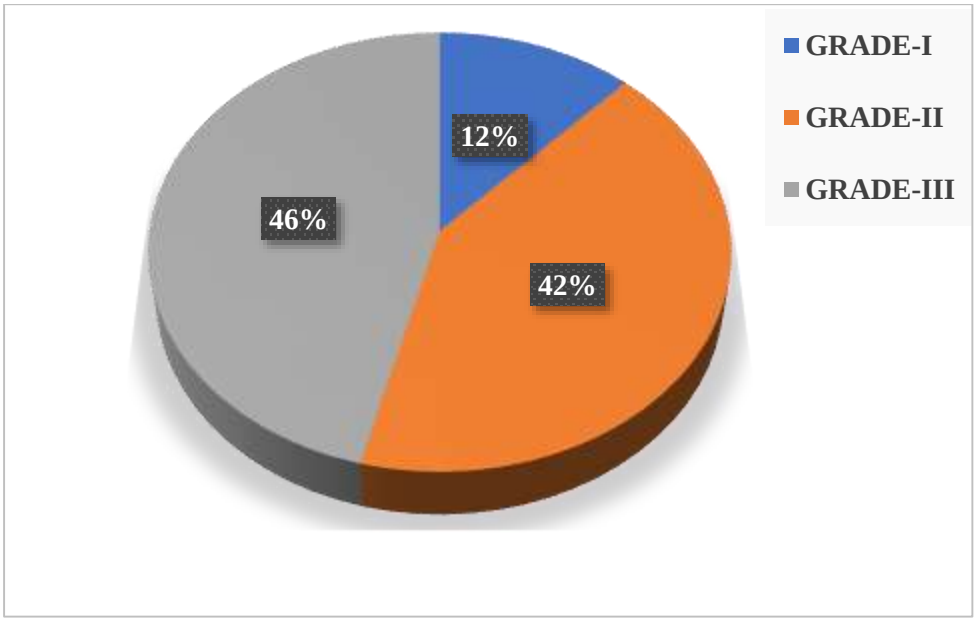


In present study majority of study population 46(92%) Perineural invasion (PNI) was absent while only in 4(8%) perineural invasion was present.

Table 26:- Distribution of subjects according to Modified Scarf Bloom Richarson Grading

Modified Scarf Bloom Richarson Grading	Frequency	Percent
GRADE-I	6	12
GRADE-II	21	42
GRADE-III	23	46

Chart 13:- Pie diagram showing distribution of subjects according to Modified Scarf Bloom Richarson Grading

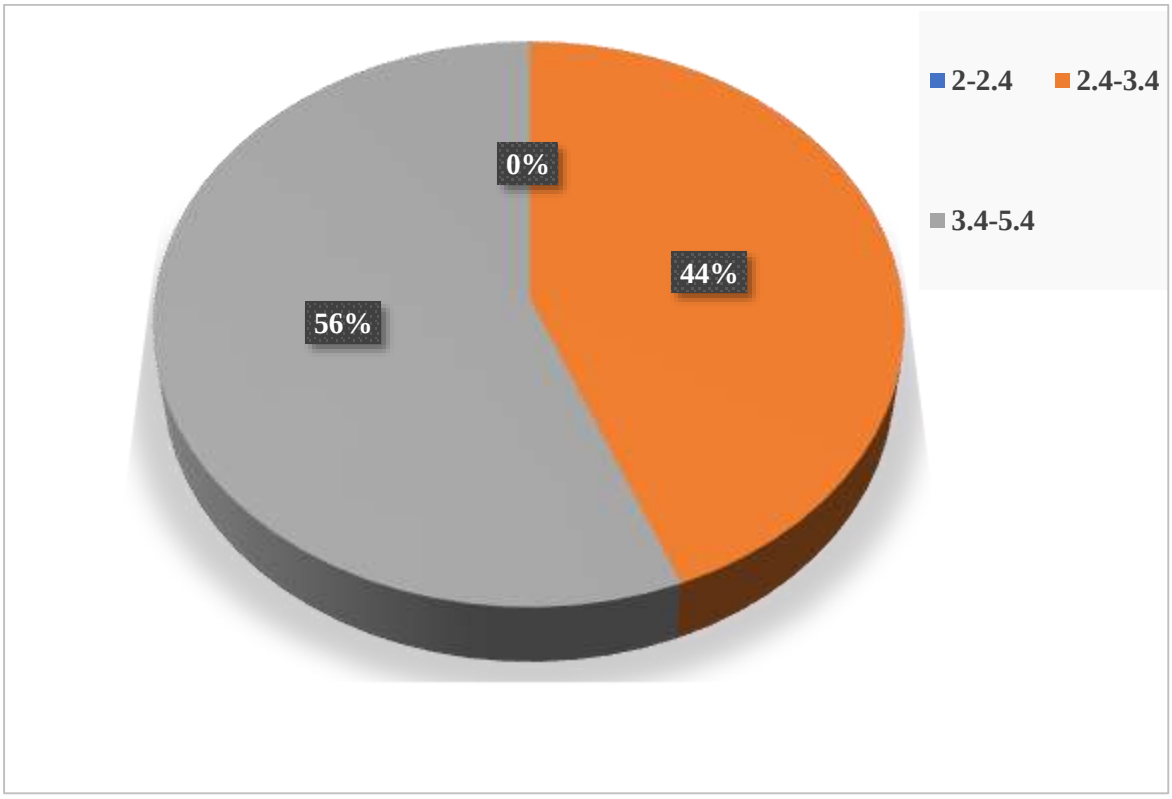


In present study, 23(46%) study population fell under Grade III followed by 21(42%) were Grade II and 6(12%) were Grade I. Most of the cases were Grade III.

Table 27: -Distribution of subjects according to NPI (Nottingham Prognostic Index)

NPI	Frequency	Percent
2-2.4	0	0
2.4-3.4	22	44
3.4-5.4	28	46

Chart 14: - Pie diagram showing distribution of subjects according to NPI (Nottingham Prognostic Index)

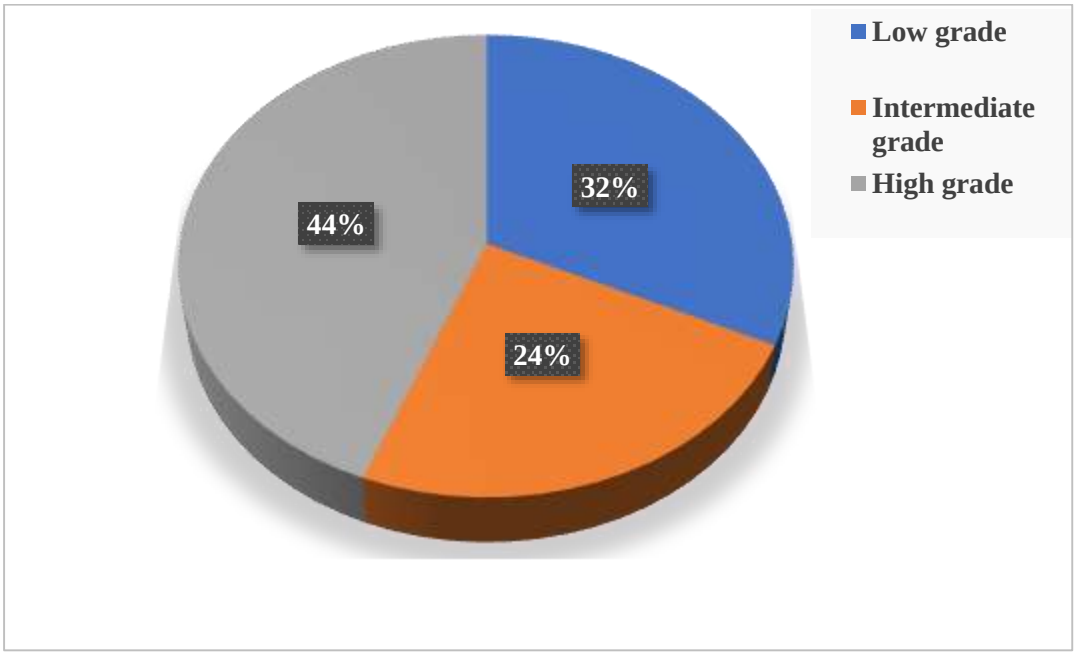


In present study 22(44%) of study population had Moderate NPI 2.4-3.4 and 28(56%) had Poor NPI. Majority of study population fell under moderate prognostic group.

Table 28:- Distribution of subjects according to Tumour Infiltrating Lymphocytes (TILS)

TILS	Frequency	Percent
Low grade	16	32.0
Intermediate grade	12	24.0
High grade	22	44.0

Chart 15:- Pie diagram showing distribution of subjects according to TILS

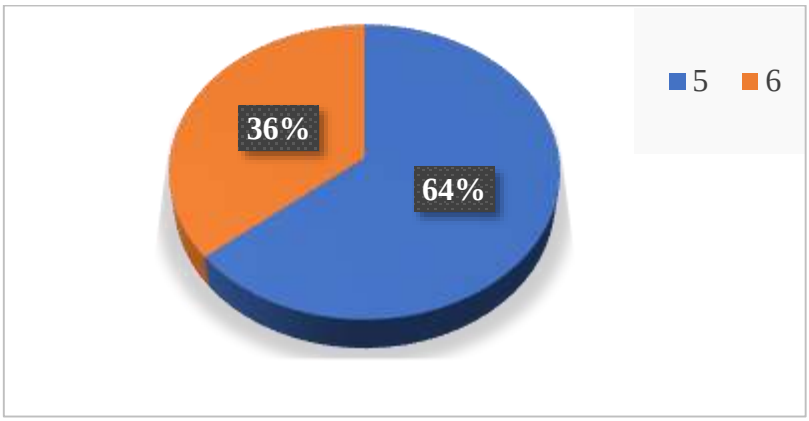


In present study 22(44%) of study population had High grade TILS, 16(32%) had low grade TILS, whereas 12(24%) had intermediate TILS. Majority of study population had high grade TILS indicate improved survival and high rate of complete response following treatment.

Table 29: - Distribution of subjects according to IHC scoring

Laminin 332 IHC scoring	Frequency	Percent
5	32	64.0
6	18	36.0
Total	50	100.0

Chart 16:- Pie diagram showing the Distribution of subjects according to IHC scoring



In present study intensity score and proportionate score was calculated independently and added together, score was obtained, this score was given grades and final grade was obtained. This IHC scoring was compared with clinicopathological parameters.

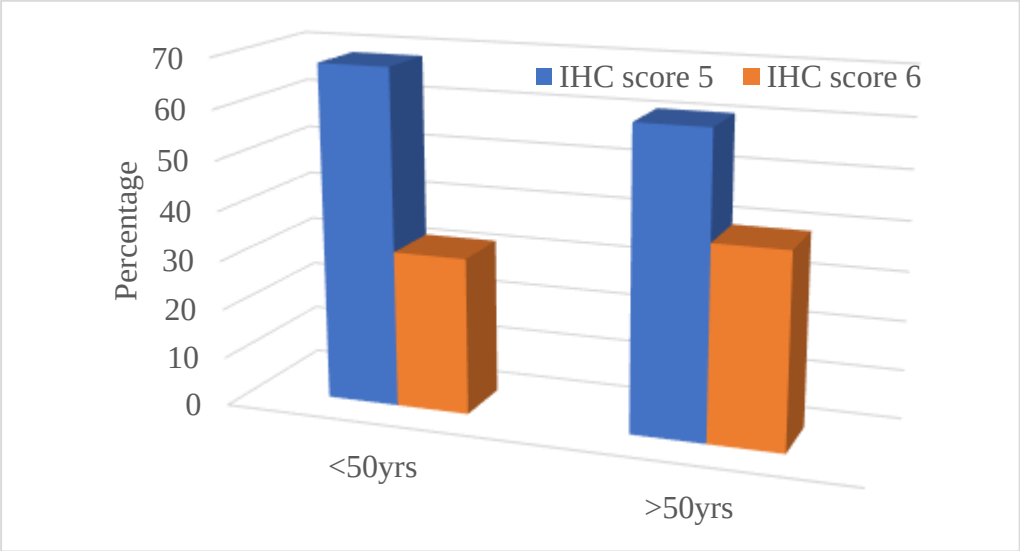
In current study all subjects had Grade 2 having IHC Laminin 332 score between 3-6.

In present study Laminin 332 IHC expression was seen in all study population, out of this 32(64%) of study population had Laminin 332 IHC score of 5 and 18(36%) had IHC scoring of 6. Majority of study population had Laminin 332 IHC score of 5.

Table 30: - Distribution of subjects according to LAMININ 332 IHC SCORE and age group

AGE	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
<50yrs	15	68.2%	7	31.8%	0.803
>50yrs	17	60.7%	11	39.3%	

Chart 17:- Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and age group

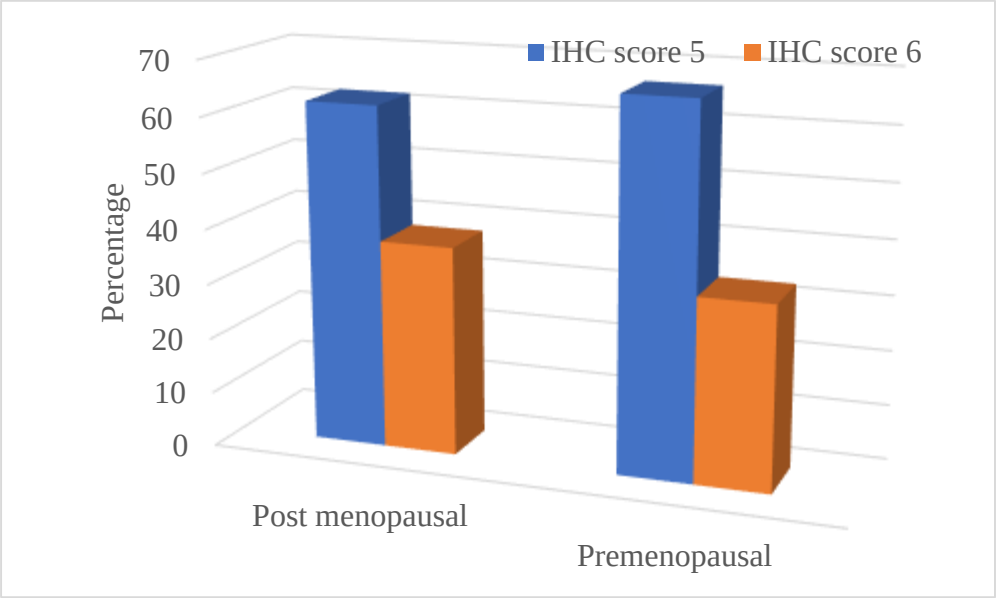


In present study 15(68.2%) of the study population expressed Laminin IHC score of 5 and 7(31.8%) expressed Laminin IHC score of 6 were <50 years age group and 17(60.7%) of study population expressed Laminin IHC score of 5 and 11(39.3%) expressed Laminin IHC score of 6 were >55 years age group. But it was discovered that there was no significant correlation between Laminin 332 IHC and the age groups with *p* Value 0.803.

Table 31: - Distribution of subjects according to LAMININ 332 IHC SCORE and menopausal status

Menopausal status	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
Post menopausal	18	62.1%	11	37.9%	0.774
Premenopausal	14	66.7%	7	33.3%	

Chart 18:- Bar diagram showing the Distribution of subjects according to IHC SCORE LAMININ 332 and menopausal status

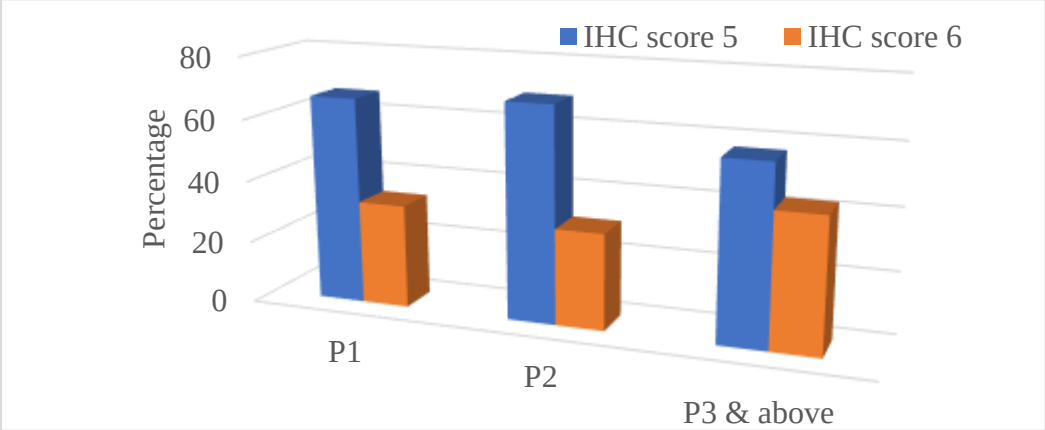


In present study 18(62.1%) of postmenopausal subjects expressed Laminin 332 IHC score 5 and 11(37.9%) expressed Laminin 332 IHC score of 6, while 14(66.7%) of premenopausal subjects expressed Laminin 332 IHC of 5 and 7(33.3%) expressed Laminin 332 IHC score of 6. There was no statistically significant difference found between Laminin 332 IHC SCORE and menopausal status with *p* Value = 0.774.

Table 33: - Distribution of subjects according to IHC SCORE LAMININ 332 and parity

PARITY	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
P1	2	66.7%	1	33.3%	0.688
P2	18	69.2%	8	30.8%	
P3 & above	12	57.1%	9	42.9%	

Chart 19: - Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and parity

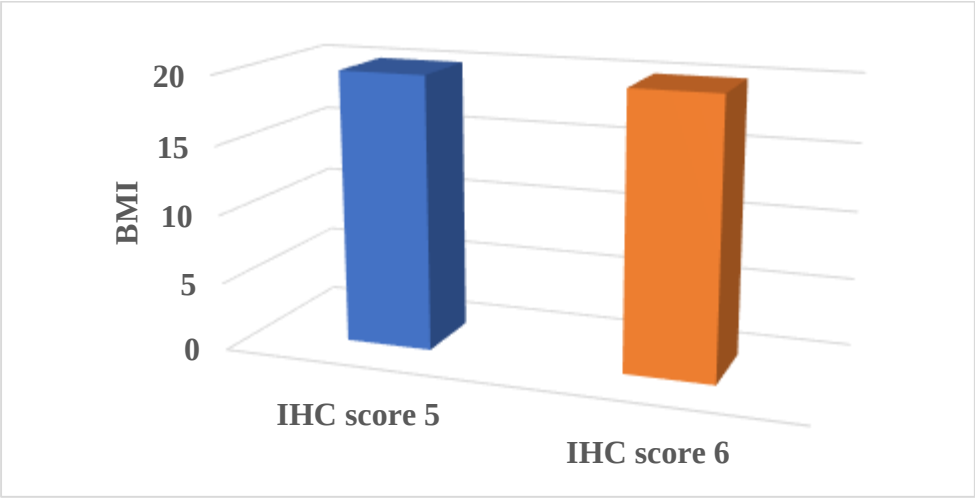


In present study 2(66.7%) and 1(33.3%) were primiparous expressed Laminin 332 IHC score 5 and 6 respectively. 18(69.2%) and 8(30.8%) were para 2 expressed Laminin 332 IHC score of 5 and 6 respectively, while 12(57.1%) and 9(42.9%) were para 3 and above expressing Laminin 332 IHC of 5 and 6 respectively. There was no statistically significant difference found between IHC SCORE and parity with *p* Value 0.688.

Table 34: - Comparison of mean BMI according to IHC score

Laminin IHC score	BMI		*p* Value
	Mean	Std. Deviation	
IHC score 5	20.00	2.229	0.929
IHC score 6	19.94	1.862	

Chart 20: - Bar diagram showing Comparison of mean BMI according to IHC score

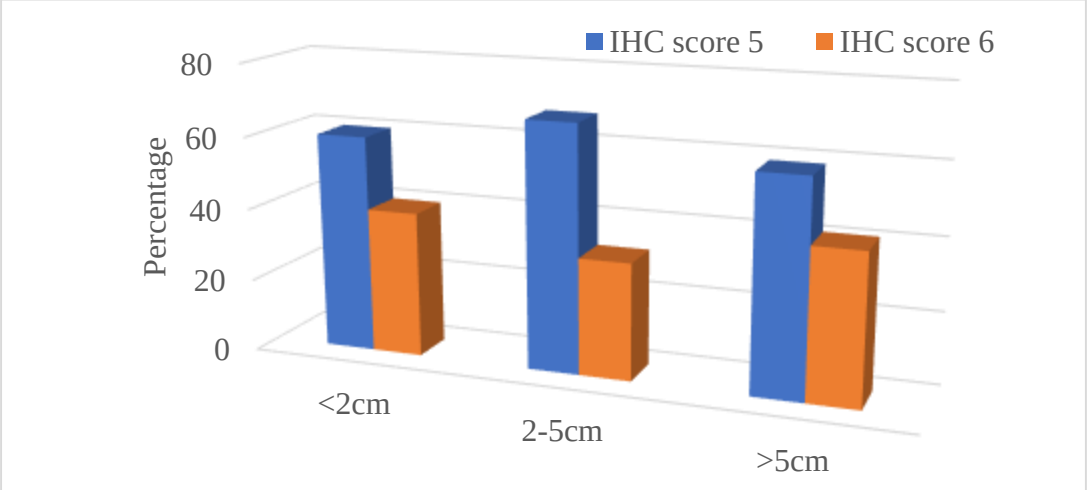


In current study, Mean BMI of Laminin 332 IHC score 5 was 20.00 whereas Mean BMI Laminin 332 IHC score of 6 was 19.94. There was no statistically significant difference found between IHC score and BMI with *p* Value 0.929.

Table 35: - Distribution of subjects according to LAMININ 332 IHC SCORE and size

Tumour size	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
<2cm	3	60.0%	2	40.0%	0.813
2-5cm	19	67.9%	9	32.1%	
>5cm	10	58.8%	7	41.2%	

Chart 21:- Bar diagram showing the Distribution of subjects according to IHC SCORE LAMININ 332 and size

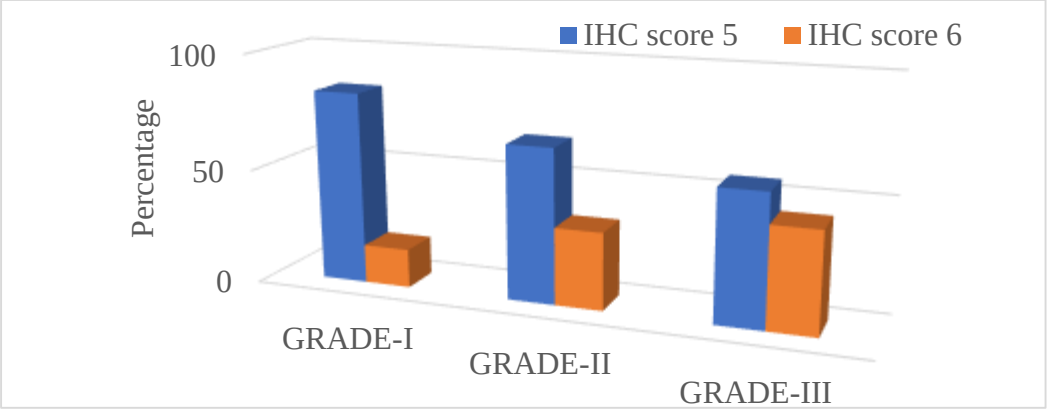


In present study 3(60.0%) and 2(40.0%) study population had tumor size <2 cms expressed Laminin 332 IHC score 5 and 6 respectively. 19(67.9%) and 9(32.1%) had tumor size 2-5 cms expressed Laminin 332 IHC score of 5 and 6 respectively, while 10(58.8%) and 7(41.2%) had tumor size >5cms expressing Laminin 332 IHC of 5 and 6 respectively. There was no statistically significant difference found between IHC SCORE and size with *p* Value 0.813.

Table 36: - Distribution of subjects according to IHC SCORE LAMININ 332 and Modified Scarf Bloom Richardson grade (MBR grade)

MSBR Grade	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
GRADE-I	5	83.3%	1	16.7%	0.450
GRADE-II	14	66.7%	7	33.3%	
GRADE-III	13	56.5%	10	43.5%	

Chart 22: - Bar diagram showing distribution of subjects according to IHC SCORE LAMININ 332 and Modified Bloom Rchardson Grade



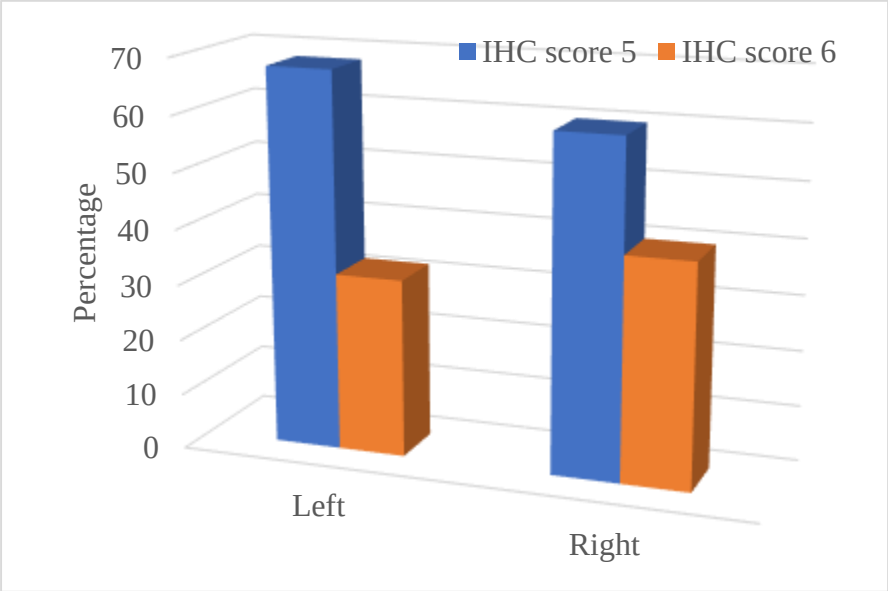
In present study 5(83.3%) and 1(16.7%) study population had MSBR Grade-1 expressed Laminin 332 IHC score 5 and 6 respectively. 14(66.7%) and 7(33.3%) had MSBR Grade 2 expressed Laminin 332 IHC score of 5 and 6 respectively, while 13(56.5%) and 10(43.5%) had Grade 3 expressing Laminin 332 IHC of 5 and 6 respectively.

There was no statistically significant difference found between Laminin 332 IHC SCORE and Modified Bloom Richardson grade with *p* value 0.450.

Table 37: - Distribution of subjects according to IHC SCORE LAMININ 332 and laterality

Laterality	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
Left	17	68.0%	8	32.0%	0.769
Right	15	60.0%	10	40.0%	

Chart 23: - Bar diagram showing distribution of subjects according to IHC SCORE LAMININ 332 and laterality of tumor



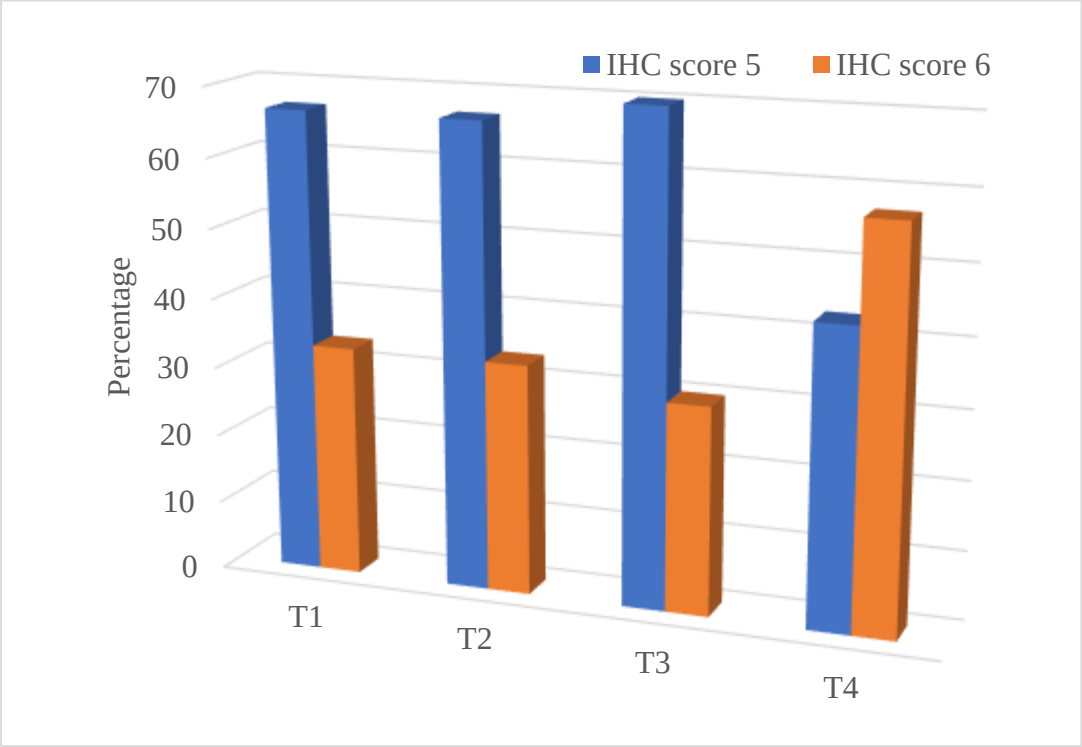
In present study 17(68.0%) of study population had tumour on Left side expressed Laminin 332 IHC score 5 and 8(32.0%) expressed Laminin 332 IHC score of 6, while 15(60.0%) of them had tumour on Right side expressed Laminin 332 IHC of 5 and 10(40.0%) expressed Laminin 332 IHC score of 6.

There was no statistically significant difference found between Laminin 332 IHC SCORE and laterality of tumour with *p* Value 0.769.

Table 38: - Distribution of subjects according to IHC SCORE LAMININ 332 and pT stage

pT stage	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
pT1	4	66.7%	2	33.3%	
pT2	18	66.7%	9	33.3%	
pT3	7	70.0%	3	30.0%	0.656
pT4	3	42.9%	4	57.1%	

Chart 24: - Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and pT stage

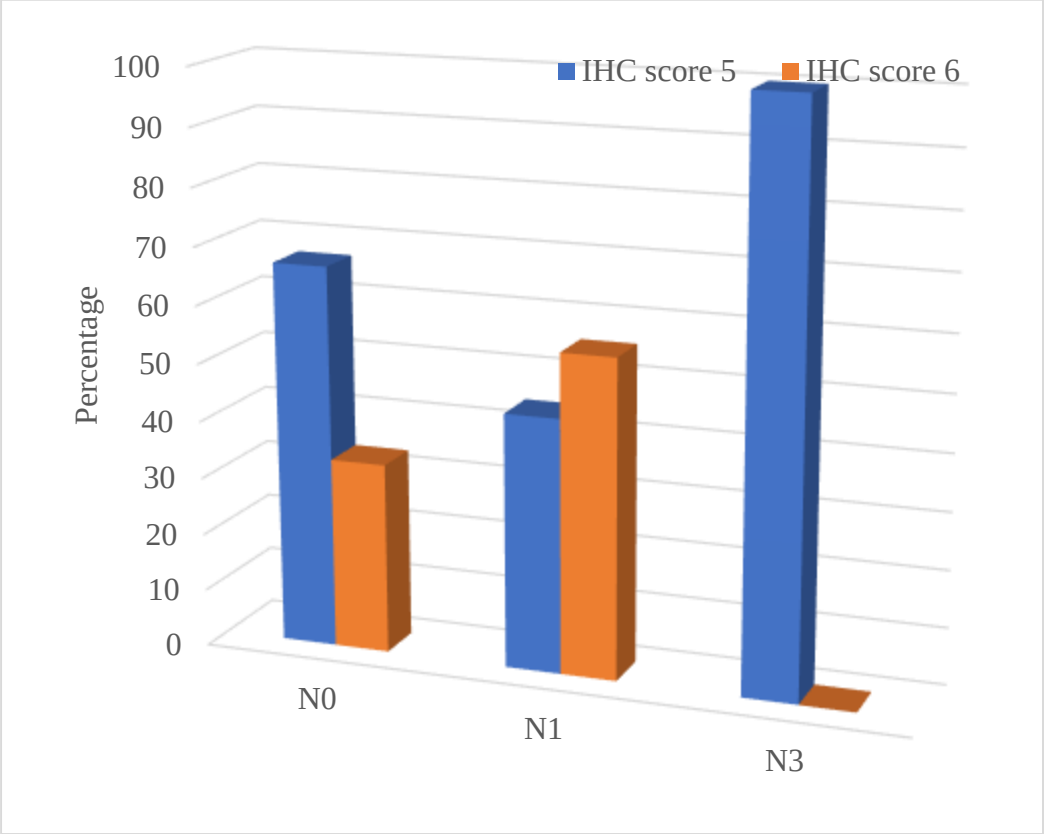


In present study 4(66.7%) and 2(33.3%) were pT1 stage expressed Laminin 332 IHC score 5 and 6 respectively. 18(69.2%) and 9(33.3%) fell under pT2 stage expressed Laminin 332 IHC score of 5 and 6 respectively, while 7(70.0%) and 3(30.0%) are pT3 stage expressing Laminin 332 IHC of 5 and 6 respectively and 3(42.9%) and 4(57.1%) study population had pT4 stage. There was no statistically significant difference found between IHC SCORE and pT stage with *p* Value 0.656.

Table 39: - Distribution of subjects according to IHC SCORE LAMININ 332 and pN stage

pN Stage	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
N0	26	66.7%	13	33.3%	0.254
N1	4	44.4%	5	55.6%	
N3	2	100.0%	0	0.0%	

Chart 25: - Bar diagram showing Distribution of subjects according to Laminin 332 IHC SCORE and pN stage



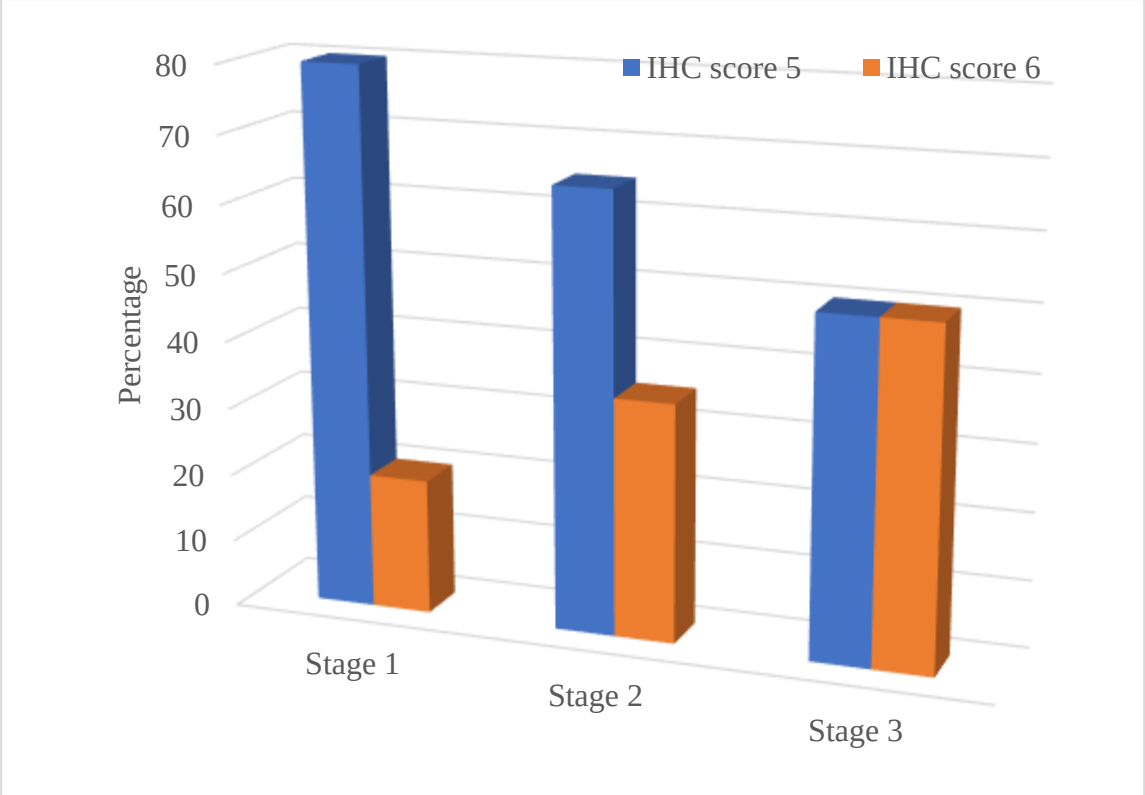
In present study 26(66.7%) and 13(33.3%) study population had pN0 stage expressed Laminin 332 IHC score 5 and 6 respectively. 4(44.6%) and 5(55.6%) had pN1 stage expressed Laminin 332 IHC score of 5 and 6 respectively, while 2(100%) had pN3 stage expressing only Laminin 332 IHC of 5.

There was no statistically significant difference found between Laminin 332 IHC SCORE and pN stage with *p* value 0.254.

Table 40: - Distribution of subjects according to IHC SCORE LAMININ 332 and pTNM stage

pTNM Stage	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
Stage 1	4	80%	1	20%	
Stage 2	24	64.8%	13	35.2%	
Stage 3	4	50%	4	50%	0.294

Chart 26: - Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and pTNM stage



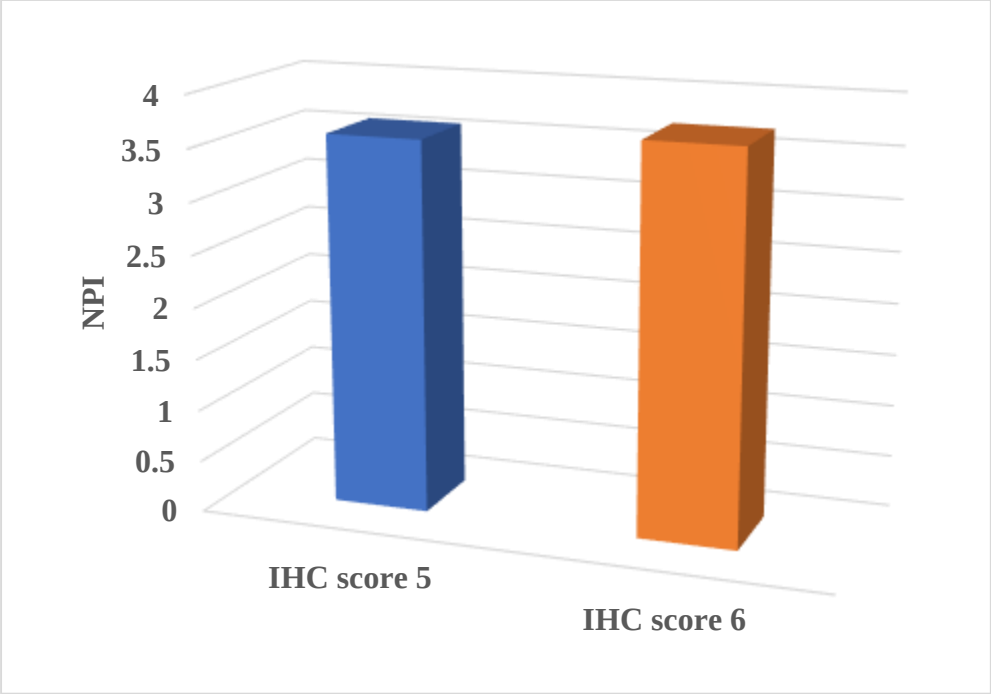
In present study 4(80%) and 1(20%) study population had pTNM Stage I expressed Laminin 332 IHC score 5 and 6 respectively. 24(64.8%) and 13(35.2%) had pTNM Stage II expressed Laminin 332 IHC score of 5 and 6 respectively, while 4(50%) and 4(50%) had pTNM Stage III expressing Laminin 332 IHC of 5 and 6 respectively.

There was no statistically significant difference found between Laminine 332 IHC SCORE and pTNM Stage with *p* value 0.294.

Table 41: - Comparison of mean NPI according to Laminin 332 IHC score

Laminin 332 IHC score	**NPI**		***p* Value**
	Mean	Std. Deviation	0.554
IHC score 5	3.587	.6705	
IHC score 6	3.711	.7145	

Chart 27: - Bar diagram showing comparison of mean NPI according to Laminin 332 IHC score

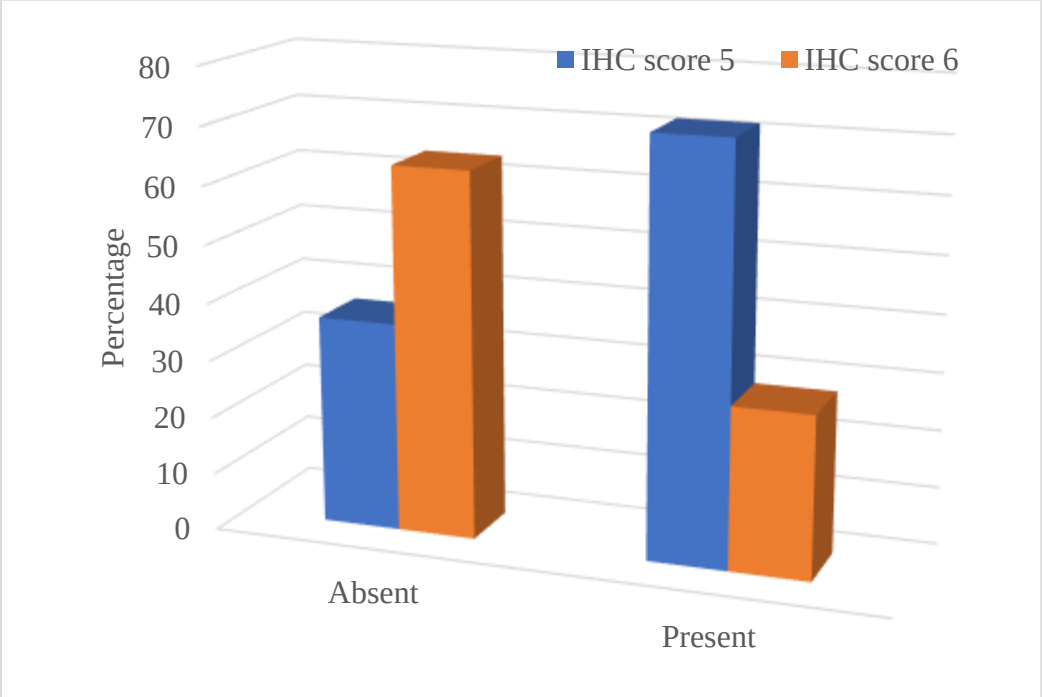


In present study Laminin 332 IHC score of 5 showed a significantly lower mean NPI (3.587) than those with an IHC score of 6 (3.711). This indicated a slightly better prognosis in the IHC score 5 group, as a lower NPI indicates better outcomes. Nevertheless, there was no statistically significant difference between the IHC score and the NPI with *p* Value = 0.554.

Table 42: - Distribution of subjects according to IHC SCORE LAMININ 332 and LVI

LVI	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
Absent	4	36.4%	7	63.6%	0.041
Present	28	71.8%	11	28.2%	

Chart 28: - Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and LVI

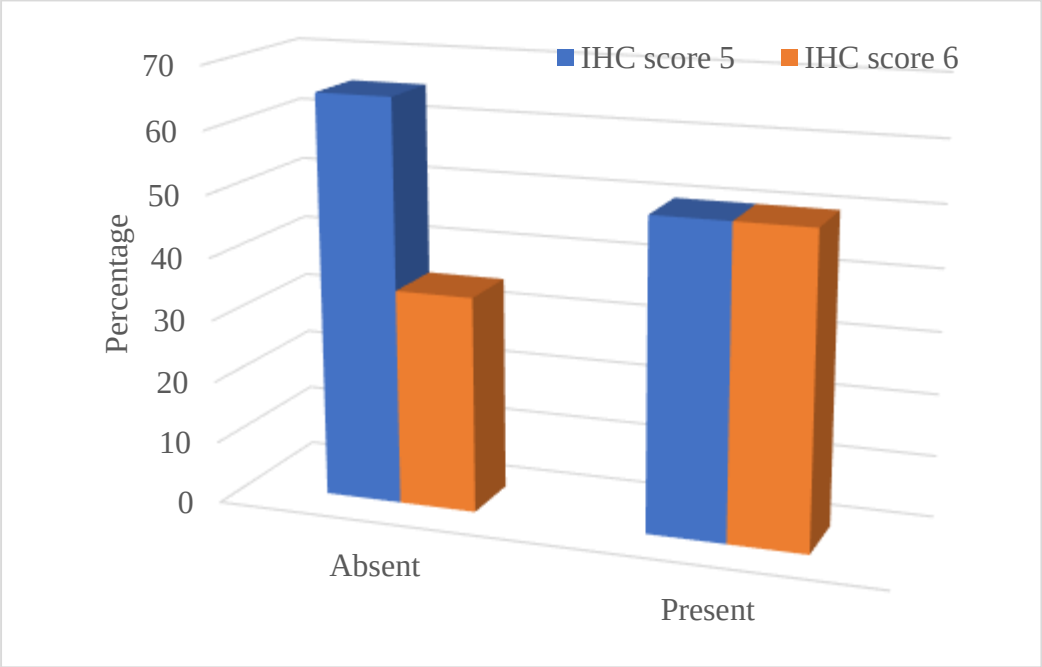


In present study Laminin 332 IHC Score 5 was more frequently related to the presence of LVI (71.8%), while IHC Score 6 was associated with the absence of LVI (63.6%). There is statistically significant association between inverse association between LVI and Laminin 332 IHC score with *p* Value 0.041.

Table 43: - Distribution of subjects according to IHC SCORE LAMININ 332 and PNI

PNI	IHC score 5		IHC score 6		*p* Value
	N	%	N	%	
Absent	30	65.2%	16	34.8%	0.612
Present	2	50.0%	2	50.0%	

Chart 29: - Bar diagram showing Distribution of subjects according to IHC SCORE LAMININ 332 and PNI

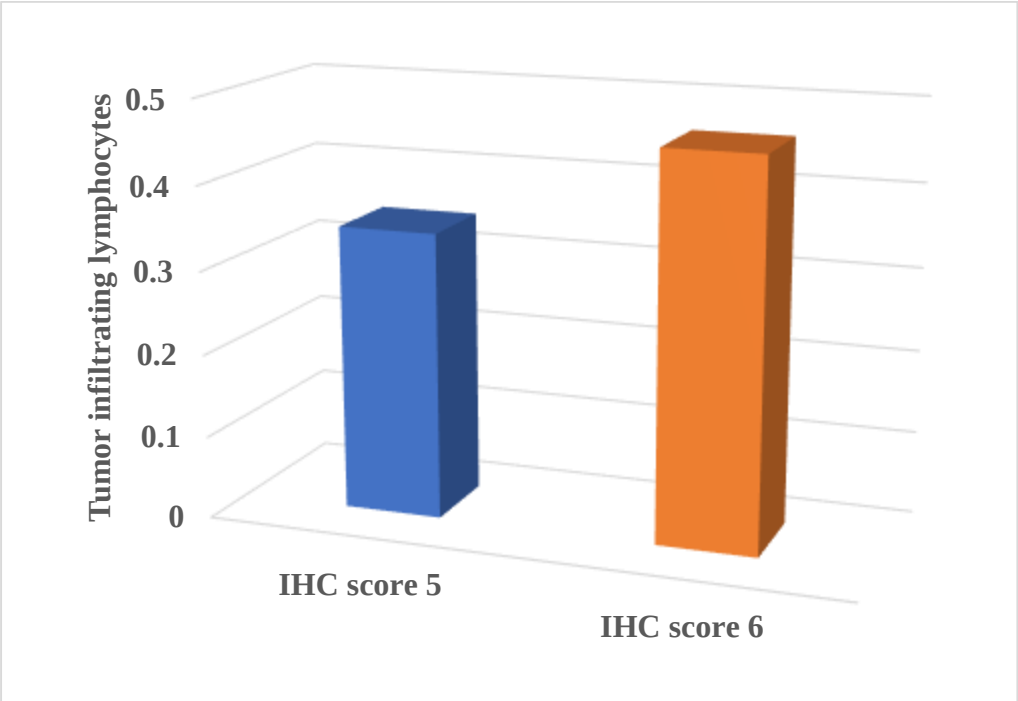


In present study presence of PNI 2(50%) and 2(50%) was equally distributed among IHC Scores of 5 and 6. 30(65.2%) and 16(34.8%) study population PNI was absent with Laminin 332 IHC Score of 5 and 6 respectively. There was no statistically significant difference found between IHC SCORE and PNI with *p* Value 0.612.

Table 44: - Comparison of mean tumor infiltrating lymphocytes according to IHC score

LAMININ 332 IHC SCORE	TUMOUR INFILTRATING LYMPHOCYTES		*p* Value
	Mean	Std. Deviation	
IHC score 5	.3444	.29354	0.187
IHC score 6	.4606	.29582	

Chart 30: - Bar diagram showing Comparison of mean tumor-infiltrating lymphocytes according to IHC score



In present study mean Tumor-Infiltrating Lymphocytes Score according to Laminin IHC score 6 (.4606) was more than Laminin IHC score 5(.3444).

There was no statistically significant difference found between the IHC score and Tumor-Infiltrating Lymphocytes with *p* Value 0.187.

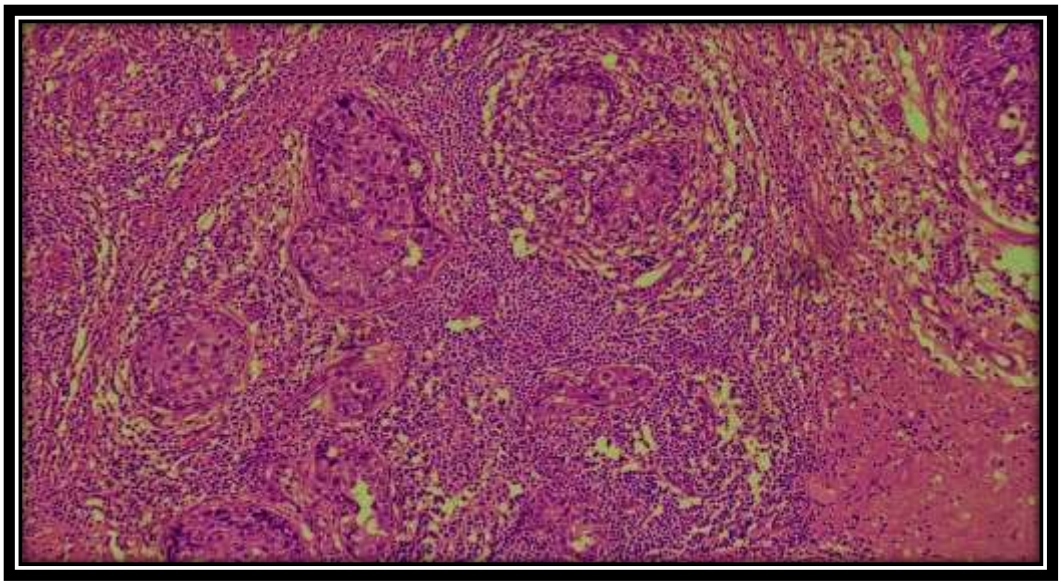


Figure 16: Microphotograph of Well Differentiated IDC(Grade-1): showing tumour cells arranged in nests and in sheets, individual tumour cells are round to oval with increased N:C ratio, with mild pleomorphic vesicular nuclei having prominent nucleoli. Few mitotic figures are seen. **(H&E, 400X)**

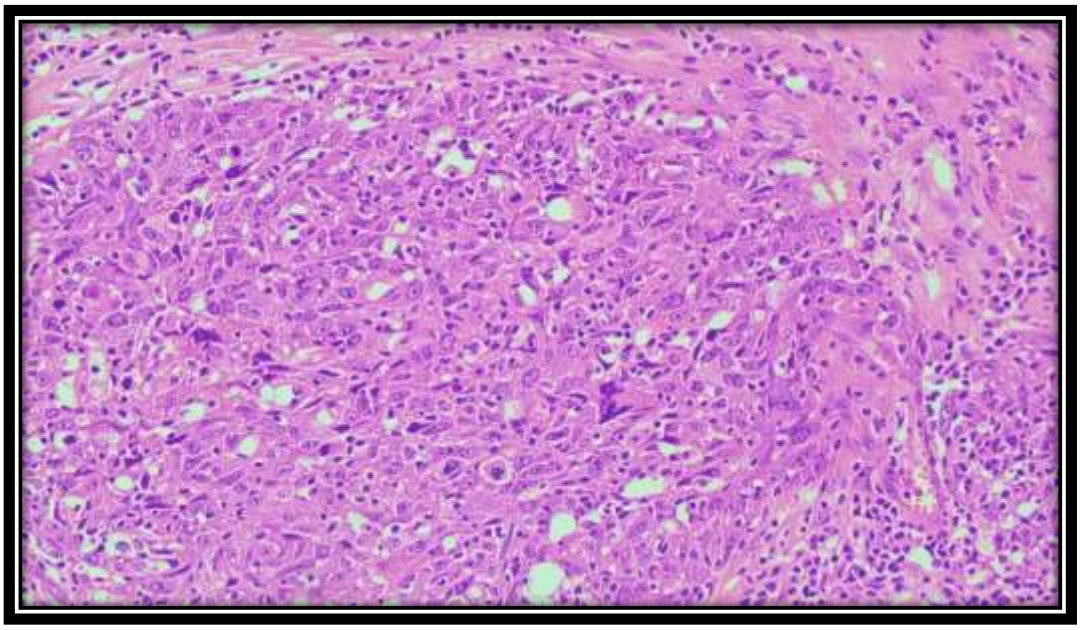


Figure 17: Microphotograph of Moderately Differentiated IDC(Grade-2): Showing tumour cells arranged in nests and in sheets, individual cells are round to oval with increased N:C ratio, moderate pleomorphic vesicular nuclei having prominent nucleoli. 7-8 Mitotic figures/10 HPF are seen. **(H&E, 400X)**

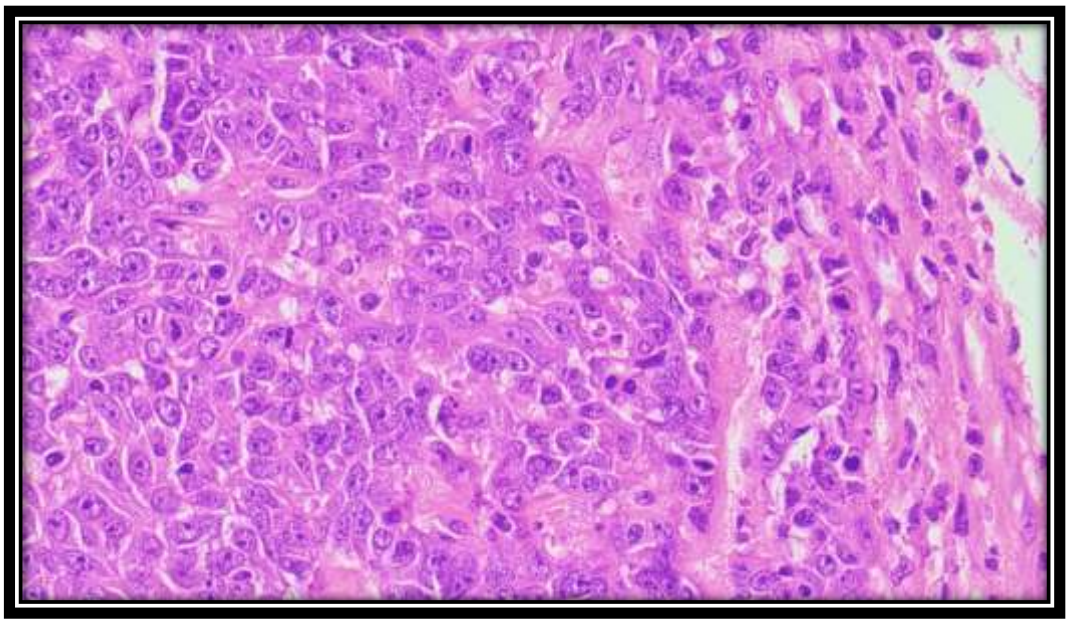


Figure 18: Microphotograph of Poorly Differentiated IDC(Grade-3): Showing tumor cells arranged in nests and in sheets, individual cells are round to oval with increased N:C ratio, highly pleomorphic vesicular nuclei having prominent nucleoli. Also seen 11-12 Mitotic figures /10 HPF. **(H&E, 400X)**

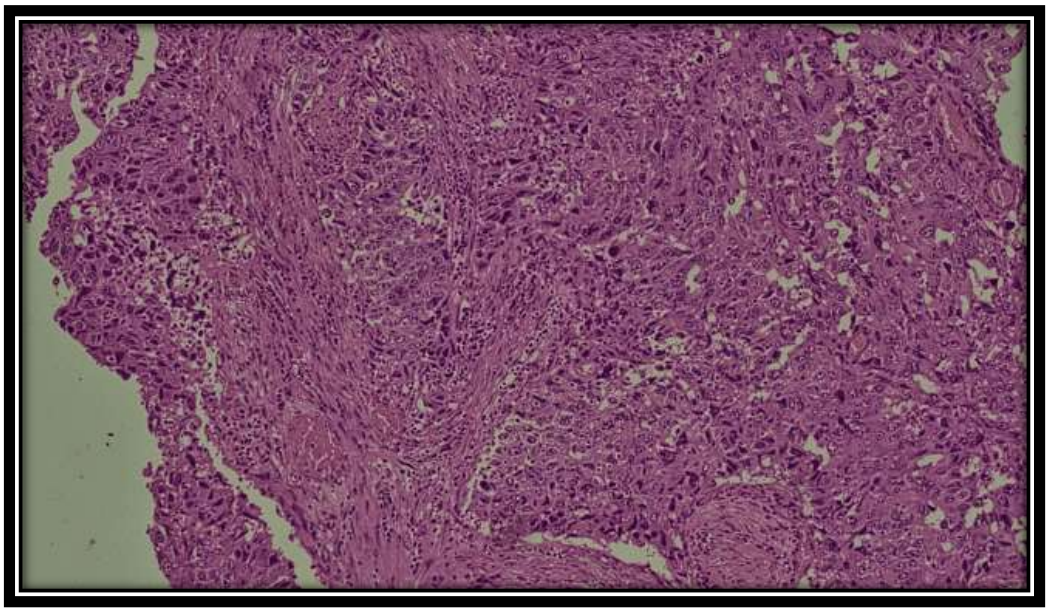


Figure 19: Microphotograph showing Perineural Invasion. (H&E, 200X)

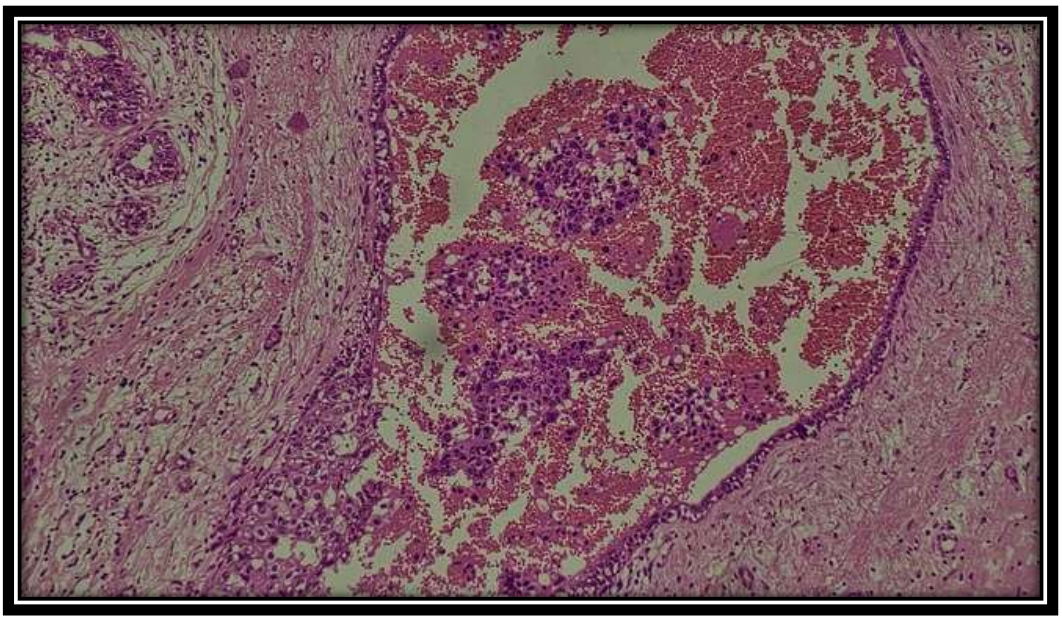


Figure 20: Microphotograph showing Lymphovascular Invasion (H&E, 200X)

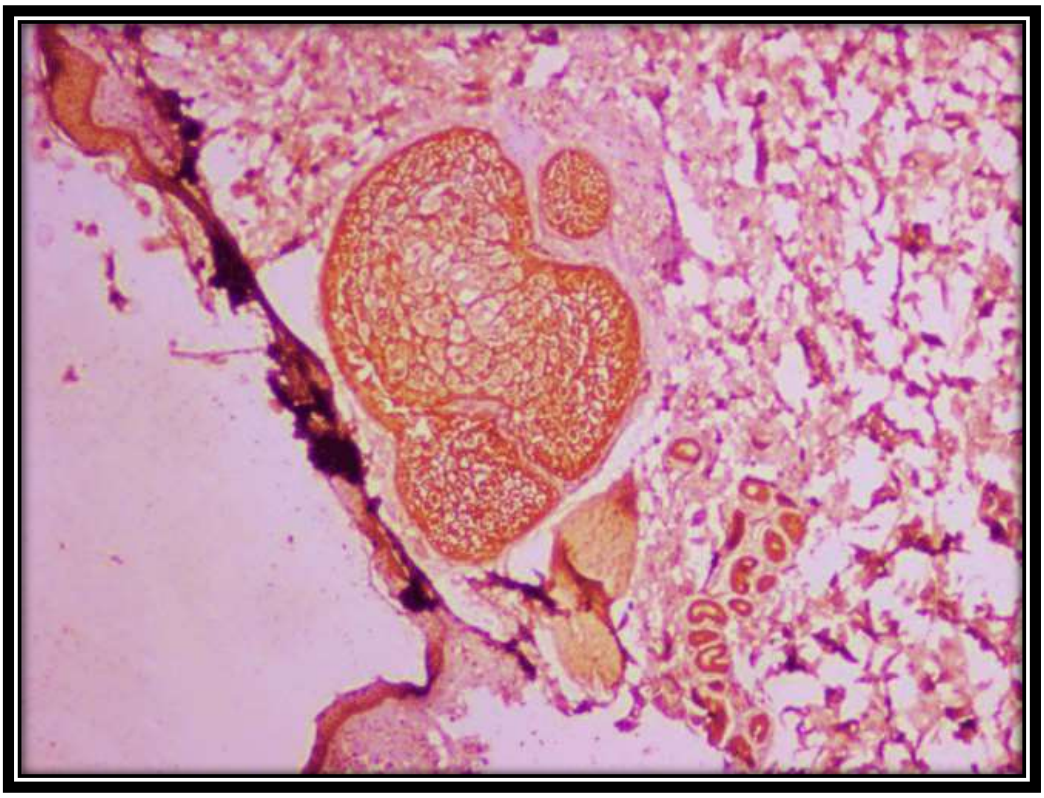


Figure 21: Microphotograph showing Skin as Positive control (Laminin 332, 200X)

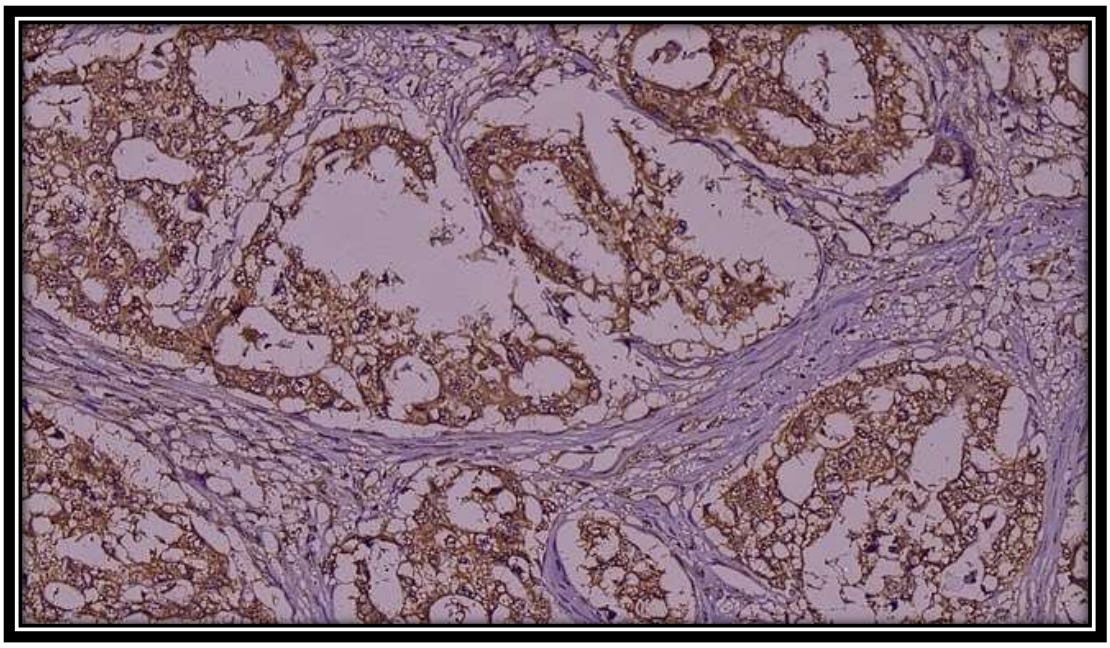


Figure 22: Microphotograph showing weak intensity(light yellow) and low proportion of Laminin IHC staining. (Laminin 332 IHC, 400X)

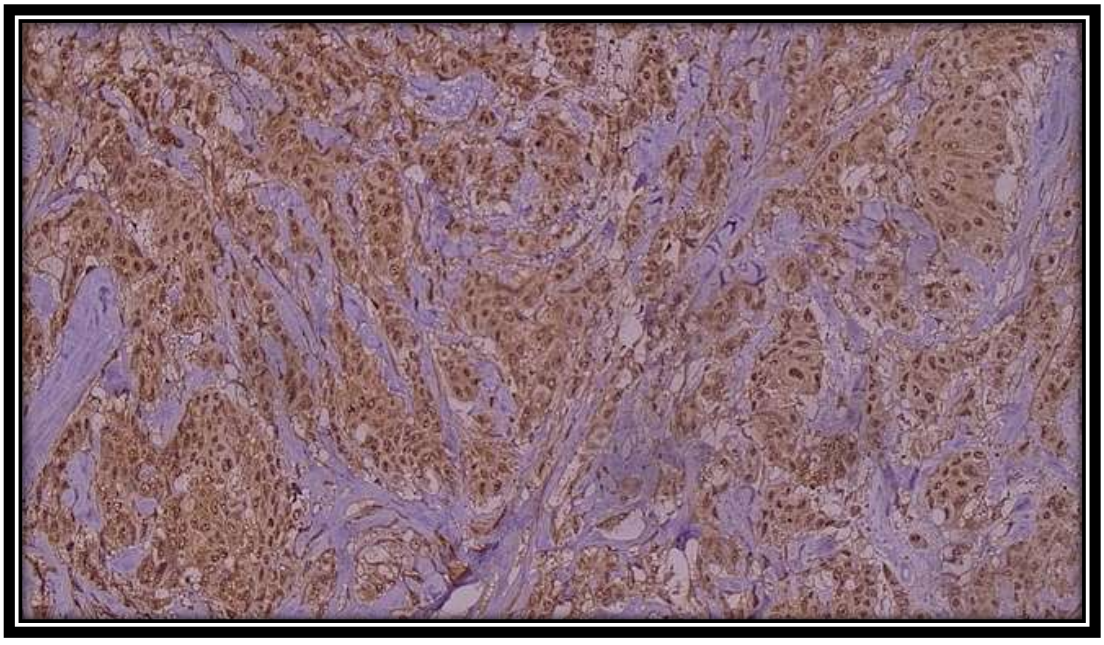


Figure 23: Microphotograph showing moderate intensity(yellow/brown) and intermediate proportion of Laminin IHC staining. (Laminin 332 IHC, 400X)

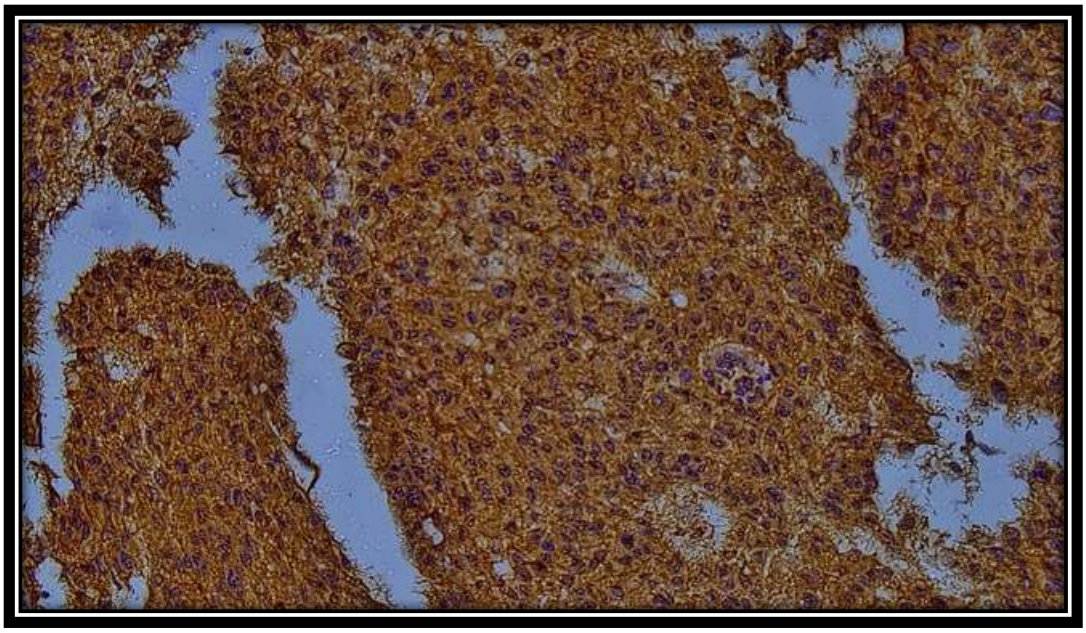


Figure 24: Microphotograph showing Strong intensity(brown) and high proportion of Laminin IHC staining. (Laminin 332 IHC, 400X)

DISCUSSION

DISCUSSION

Triple-negative breast carcinomas, especially basal-like type, are aggressive. Laminin, a diagnostic molecule, serves as a prognostic marker. Its staining pattern changes from regular and linear in non-neoplastic breast tissue to irregular and disrupted in carcinomas.[5]

In invasive ductal carcinoma (IDC), laminin staining reveals basement membrane material around tumor cell groups, suggesting tumor cells produce laminin. This indicates variable ability to produce basement membrane components, with stroma playing a role in synthesis. Laminin 332 is highly expressed in epithelial tumors, accumulating at the tumor-stroma interface.[151]

Breast carcinomas exhibit heterogeneous laminin distribution, with production limited to tumor cells adjacent to stroma, indicating stroma's role in basement membrane synthesis. This pattern varies across histologic types and differentiation degrees.[151]

In the present study, a total number of 50 TNBC cases were studied. Association between histopathological parameters and Laminin 332 immunostaining were studied.

AGE:

Table 45: - Comparison of Present study with other studies with respect to mean, median age and percentage

STUDIES	YEAR	MEAN	MEDIAN	PERCENTAGE	
Present Study	2025	50.3 yrs	54.5 yrs	<50 yrs	>50yrs
				44%	56%
Gadhia PK et al[164]	2024	-	55 yrs	-	-
Rath G et al[5]	2023	-	-	10.71%	89.29%
Memon et al[165]	2023	46.07±11.32	-	-	-
Sarin et al[167]	2016	-	-	60%	40%
Sajid et al[166]	2014	46.3 yrs	-	65.9%	44.1%
Lakshmaiah KC et al[171]	2014	-	-	72.61%	27.38%
Dent,Rebecca et al[169]	2007	53	-	-	-
Rakha, Emad A et al[170]	2007	-	49.9	-	-
Carey L. A et al[168]	2006	46±10	-	-	-

- In present study, 56% of study population were >50 years, and 44% of patients were > 50 years. The median age is 54.5 years, and mean age was 50.3 years.
- Present study was in concordance with studies conducted by Rath G et al [5], Gadhia PK et al[164], Dent, Rebecca et al[169]
- Present study was in discordance with Memon et al[165], Sajid et al[166], Sarin et al[167], Carey L. A., et al [168], Rakha, Emad A. et al.[170], and Lakshmaiah, KC, et al[171].

Table 46:- Comparison of prevalence of TNBC in present study with other studies based on parity status

Studies	**Year**	**Parity**	
		Primi para (P1)/Low parity	Multi para (P2 and above)/High parity
Present study	2025	6%	(96%)
Kumar N et al[172]	2024	-	Predominant*
Memon BA et al[165]	2023	-	Predominant*
Fortner RT et al[173]	2019	13%	77%
Lakshmaiah KC et al[171]	2014	-	Predominant*
Shinde SS et al[174]	2010	-	Predominant*

In Present study majority (96%)of patients were multiparous which was in concordance with studies done by Fortner RT et al[175] , 77% were multipara and studies by Kumar N et al.[173], Memon BA et al.[165], Shinde SS et al.[174] and Lakshmaiah KC et al.[171] majority

of study population were multipara. Multiparity was associated with increased risk of TNBC.

*Did not specify percentages

Table 47:- Comparison of present study with other studies with respect to menopausal status

Studies	Year	Menopausal status (%)	
		Premenopausal	Post menopausal
Present Study	2025	42%	58%
Nishimura R et al[175]	2022	25.3%	74.7%
Sable M et al[176]	2017	37.6%	54.7%
Lakshmaiah KC et al[171]	2014	40.47%	59.52%
Carey L. A et al[168]	2006	64%	36%

- In present study, 29(58%) of study population were post-menopausal compared to 21(42%) of premenopausal patients.
- Present study was in concordance with studies conducted by Nishimura R. et al.[175] where majority 74.7% were in postmenopausal phase and 25.3% in premenopausal phase, Sable M et al.[176] 54.7% were in postmenopausal phase and 37.6% are in premenopausal phase, Lakshmaiah KC et al.[171], 59.52% were postmenopausal and 40.47% were in premenopausal phase and risk of TNBC was high in postmenopausal compared with women in premenopausal phase.
- Present study was in discordance with study conducted by Carey L. A. et al.[168] where majority were premenopausal 64% compared to 36% postmenopausal phase.

Table 48: - Comparison of present study with other studies according to Laterality of Tumour

Studies	Year	Laterality	
		Right side	Left side
Present Study	2025	50%	50%
Gadhia PK et al[164]	2024	30.88%	69.12%
Lakshmaiah KC et al[171]	2014	41.7%	58.3%

- In present study, there was equal distribution of tumour in Right 25(50%) and Left breast 25(50%).
- Studies done by Gadhia et al.[164]majority (69.12%) had tumor in Left breast compared with right breast (30.88%) and study by Lakshmaiah KC et al.[171] documented Left breast predominance (58.3%) compared to right breast (41.7%)which were not in concordance with present study.

Table 49:- Comparision of present study with other studies with respect to BMI

Studies	Year	BMI			
		Under wt.	Normal	Over Wt.	Obese
Present Study	2025	8%	84%	8%	0%
Ademuyiwa, Foluso O et al[177]	2011	29.7%	0%	31.1%	39.2%

In present study, 84% of study population had normal weight, 8% were overweight and 8% were underweight where as in study done by Ademuyiwa, Foluso O et al.[177] majority of study population 39.2% are obese which was not in concordance with present study.

Table 50:- Comparision of present study with other studies with respect to Size of the tumour

Studies	Year	Tumour Size		
		<2cm	**2-5cms**	**>5cms**
Present Study	2025	10%	56%	34%
Pankaj D et al[178]	2024	5.33%	33.33%	58.0%
Rath Get al[5]	2023	17.86	28.57%	53.57%
Gupta M et al[179]	2017	2.9%	65.7%	31.4%
Plasilova ML et al[180]	2017	46.4%	38.1%	8.4%
Lakshmaiah KC et al[171]	2014	1%	35.7%	58%
Dent, Rebecca et al[169]	2007	55.6%	36.5%	7.9%

In present study majority of study population 56% had tumour size of 2-5 cms followed by 34% having >5cms and 10% had <2cms.Study done by Gupta M et al.[179] majority had tumor size of 2-5 cms which was similar to present study.

Studies done by Pankaj D et al[178] Rath Get al[5], Lakshmaiah KC et al[171] majority of study population had tumor size of >5cms and studies done by Plasilova ML et al[180] and Dent, Rebecca et al[169] has tumor size of <2 cms which were not in concordance with present study.

Table 51:- Comparision of present study with other studies with respect to pT stage

Studies	year	pT Stage			
		pT1	pT2	pT3	pT4
Our study		12.0%	54%	20%	14%
Pankaj D et al[178]	2024	5.33%	35.33%	18%	40%
Yin L et al[181]	2018	44.8%	51.6%	2%	0%
Urru, S.A.M[182]	2018	36.7%	43.3%	6.5%	5.1%
Gangi A et al[183]	2014	43.9%	44.2%	11.9%	0%
Lakshmaiah KC et al[171]	2014	1.1%	35.75%	3.3%	25%

In present study majority 54% of study population were diagnosed at pT2 stage followed by 20% pT3 stage.

Studies done by Yin L et al.[181] Urru, S.A.M[182] Gangi A et al.[183] Lakshmaiah KC et al.[171] majority of study population were diagnosed at pT2 stage 51.6%, 43.3%, 44.2%, 35.75% respectively which were similar to present study.

Study by Pankaj D et al.[178] majority 40% were diagnosed at pT4 stage which was not in concordance with present study.

Table 52:- Comparision of present study with other studies with respect to pN Stage

Studies	year	pN Stage			
		N0	**N1**	**N2**	**N3**
Present study	2025	78%	18%	0%	4%
Pankaj D et al[178]	2024	37.33%	26.67%	32%	4%
Yin L et al[181]	2018	62.3%	21.5%	9.6%	6.4%
Gangi A et al[183]	2014	61.1%	29.5%	9.4%	0%
Wang XX et al[184]	2016	69.5%	21.9%	0%	5.2%
Plasilova ML et al[180]	2016	72%	20.1%	4.7%	3.3%

In present study majority of study population 78% had N0 stage followed by N1 (18%)and N3(4%). In studies done by Pankaj D et al.[178] Yin L et al.[181] Gangi A et al.[183] , Wang XX et al.[184] Plasilova ML et al.[180] majority of subjects had N0 stage with 37.33%, 62.3%, 61.1%, 69.5% and 72% respectively which was in concordance with present study.

Table 53:- Comparision of present study with other studies with respect to pTNM stage

Studies	Year	pTNM Stage			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
Our study	2025	5%	74%	16%	-
Pankaj D et al[178]	2024	8%	49.3%	35.3%	-
Sarin R et al[167]	2016	8.2%	53.4%	13.6%	-
Lakshmaiah KC et al[171]	2014	1.1%	41.66%	51.19%	5.9%
Suresh P et al[185]	2013	13%	62%	15%	10%
Carey L. A et al[168]	2006	2%	14%	84%	-

In present study, 74% of study population were stage II, 16% were stage III, 5% were stage I. Most common stage at which tumours were detected was stage II.

Studies conducted by Pankaj D et al.[178], Sarin R et al[167], Suresh P et al[185] majority of study population were stage II with 49.3%, 53.4%, 62% respectively which showed concordance with present study.

Studies conducted by Lakshmaiah KC et al[171], Carey L. A et al[168] majority of subjects were stage III having 51.19% and 84% respectively which was not in concordance with present study.

Table 54:- Comparision of present study with other studies with respect to histological type

Studies	Year	Histological type			
		IDC	**Poorly differentiated IDC**	**IDC - Medullary diff.**	**Others**
Present Study	2025	92%	4%	4%	-
Rath G et al[5]	2025	98.2%	-	1.79%	-
Balkenhol, M C A et al[186]	2020	88.4%	-	-	7.8%
Bonadio RC et al[187]	2022	-	-	10.6%	89.4%
Nishimura R et al[175]	2022	81.4%	-	-	19.6%
Liao HY et al[188]	2018	91.6%,	-	1.4%	7%

In present study, most common histological type was IDC 92% followed by Poorly differentiated IDC 4% and 4% IDC with medullary differentiation.

In studies by Rath G et al[5] ,Balkenhol M C A et al[186], Nishimura R et al[175] and Liao HY et al[188] also documented the most common histological type was IDC with 98.2%, 88.4%,81.4% and 91.6% which were similar to our study.

Study by Bonadio RC et al[187] most common histological type was metaplastic carcinoma which was in discordant with present study.

Table 55:- Comparison of present study with other studies with respect to Modified Scarf Bloom Richarson Grading

Studies	Year	Tumour Grade		
		Grade-1	Grade-2	Grade-3
Present Study	2025	12%	42%	46%
Benye TA et al[189]	2024	10.7%	60.9%	28.4%
Rath G et al[5]	2023	4%	16%	36%
Reddy GM et al[190]	2017	5.9%	38.2%	55.9%

In present study, 46% of study population had Grade-3, 42% had Grade-2 and 12% had Grade 1.

Studies done by Rath G et al[5] and Reddy GM et al[190] majority of study population 36% and 55.9%, respectively had Grade 3 which were in concordance with present study.

Studies done by Benye TA et al[189] majority of study population 60.9% had Grade-2 which was not in concordance with present study.

Table 56: - Comparison of present study with other studies with respect to NPI (Nottingham Prognostic Index)

Studies	Year	NPI		
		2-2.4	2.4-3.4	3.4-5.4
Present study	2025	0%	44%	46%
Widiana et al[191]	2025	17.3%	52.5%	30.2%
AI jarroudi et al[192]	2019	5.1%	55.1%	39.8%

In present study, 46% of study population had poor prognostic index with NPI 3.4 to 5.4 followed by 44% with moderate prognostic index.

Studies by Widiana et al[191] and AI jarroudi et al[192] most of study subjects had moderate prognostic index with NPI 2.4–3.4 which was not in concordance with present study.

Table 57:- Comparison of present study with other studies with respect to Tumour Infiltrating Lymphocytes (TILS)

Studies	Year	TILS		
		Low	Intermediate	High
Present Study	2025	32%	24%	44%
Leon-Ferre RA et al[193]	2024	45%	34%	21%

In present study, 44% of study population had high grade TILS, 32% had low grade TILS and 24% had intermediate grade. High grade TILS indicate good prognosis which was in contrary to study done by Leon-Ferre RA et al.[193] ,45% had low grade TILS.

Table 58:- Comparison of present study with other studies with respect to LVI

Studies	Year	LVI	
		Present	Absent
Present Study	2025	78%	22%
Urru SAM et al[182]	2018	69.8%	30.2%
Yin L et al[181]	2018	35.1%	64.9%
Ahn KJ et al[194]	2017	19.0%	81%
Plasilova ML[180]	2016	19%	81%
Gangi A et al[183]	2014	4%	96%

In present study 78% of patients, lymph vascular invasion was present and 22% of subjects lymph vascular invasion was absent. Studies by Urru SAM et al[182] majority of subjects 64.9% lymph vascular invasion was present, which was similar to present study.

Studies by Yin L et al[181] Ahn KJ et al[194] Plasilova ML[180] Gangi A et al[183] most of the subjects i,e,64.9%, 81%, 81% and 96% respectively had no lymphovascular invasion which were not in concordant with present study.

Table 59: - Comparison of present study with other studies with respect to Perineural Invasion (PNI)

Studies	Year	PNI	
		Present	Absent
Present Study	2025	8%	92%
Khanal S et al[195]	2020	15.8%	84.2%
Ahn KJ et al[194]	2017	4.8%,	95.2%

In present study, PNI was absent in 92% of study population and in 8% PNI was present, whereas studies by Khanal S et al[195] 2020 and Ahn KJ et al[194], most of the study population PNI was absent which were similar to present study.

Table 60: - Comparison of present study with other studies with respect to Laminin 332 IHC expression

Studies	Year	Laminin 332 IHC Score	
		Positive	Negative
Present Study	2025	100% - Score 5 - 64% Score 6 - 36%	0%
Rath G et al[5]	2023	53.57%	46.43%
Carpenter PM et al[158]	2018	73.2%	26.8%
Kwon, Soon-Young MD et al[157]	2012	70%	30%

In present study 100% of study population expressed Laminin 332, 32(64%) had a moderate score of 5 and 18(36%) had score of 6. Studies done by Rath G et al[5], Carpenter PM et al[158] and Kwon, Soon-Young MD et al[157] expressed Laminin 332 positivity of 53.57%, 73.2% and 70% respectively, which is not in concordance with present study.

Table 61:- Comparison of present study with other studies with respect to Laminin 332 IHC score and Age group

Studies	Year	Age group (%)	Laminin 332 IHC	
			Positive	Negative
Present Study	2025	<50 years (44%)	Score 5 -68.2% Score 6 -31.8%	0
		>50 years (56%)	Score 5 -60.7% Score 6 -39.3%	0
Rath G et al[5]	2023	<50 years (10.71%)	33.33%	66.67%
		>50 years (89.29%)	56%	44%

In present study 15(68.2%) of the study population expressed Laminin IHC score of 5 and 7(31.8%) expressed Laminin IHC score of 6 were <50 years age group and 17(60.7%) of study population expressed Laminin IHC score of 5 and 11(39.3%) expressed Laminin IHC score of 6 were >55 years age group. 100% of study population were Laminin 332 IHC positive. 56% of subjects were > 55 years expressed Laminin 332.

Study done by Rath G et al[5] 10.71 % of study population were <50 years , among them 33.33% expressed laminin 332 and 66.67% were Laminin 332 negative and 89.29 % were >50 years, 56% were laminin 332 positive and 44% were laminin 332 negative. Higher number of study population expressing laminin 332 were >50 years which is in concordance with present study.

Menopausal Status association with Laminin 332 IHC score

- In present study, 18(62.1%) of postmenopausal cases expressed Laminin 332 IHC score of 5 and 11(37.9%) cases expressed Laminin 332 IHC score of 6.
- 14(66.7%) of premenopausal subjects expressed Laminin 332 IHC of 5 and 7(33.3%) expressed Laminin 332 IHC score of 6.
- Limited published data is available in English literature on this parameter to compare.

Association of Laminin 332 IHC score with Parity

- In present study 2(66.7%) and 1(33.3%) were primiparous expressed Laminin 332 IHC score 5 and 6 respectively.
- 18(69.2%) and 8(30.8%) were para 2 expressed Laminin 332 IHC score of 5 and 6 respectively.
- 12(57.1%) and 9(42.9%) are para 3 and above expressing Laminin 332 IHC of 5 and 6 respectively. Limited data is available in English literature on this to compare.

Mean BMI association with Laminin 332 IHC score

In current study, Mean Laminin 332 IHC score of 5 was 20.00 whereas Mean Laminin 332 IHC score of 6 was 19.94. Limited published data is available in English literature on this to compare.

Table 62:- Comparison of present study with other studies with respect to Laminin 332 IHC score and Tumour Size

Studies	Year	Tumor size n (%)	Laminin 332 IHC	
			Positive	Negative
Present study	2025	<2cms 5(10%)	Score-5 (60.0%) Score-6 (40.0%)	0
		2-5cms 28(56%)	Score-5 (67.9%) Score-6 (32.1%)	0
		>5cms 17(34%)	Score-5 (58.8%) Score-6 (41.2%)	0
Rath G et al[5]	2023	< 2 cms 10(17.86%)	80%	20%
		2-5 cms 16(28.57%)	75%	25%
		>5 cms 30(53.57%)	13.33%	86.67%

In present study 28(56%) had 2-5 cms tumor size, of which 67.9% expressed laminin 332 IHC score of 5 and 32.1% expressed laminin IHC score of 6 , followed by 17(34%) had tumor size >5cms, of which 58.8% expressed IHC score of 5 and 41.2% expressed laminin 332 IHC score of 6.

Study by Rath G et al[5] 30(53.57%) had tumour size >5cms of them 86.67% are negative for laminin 332 IHC and 13.33% expressed laminin 332 IHC which was not in concordance with present study.

Table 63:- Comparison of present study with other studies with respect to Laminin 332 IHC score and Modified Bloom Richardson Grade

Studies	Year	MBR Grade n(%)	Laminin 332 IHC	
			Positive	**Negative**
Present study	2025	Grade 1-6(12%)	Score 5-83.3% Score 6-16.7%	0
		Grade 2-21(42%)	Score 5-66.7% Score 6-33.3%	0
		Grade 3-23(46%)	Score 5-56.5% Score 6-43.5%	0
Rath G et al[5]	2023	Grade 1 (7.14%)	50%	50%
		Grade 2 (28.57%)	56.25%	43.75%
		Grade 3 (64.29%)	33.33%	66.67%

In present study, 23(46%) had grade 3 of them 56.5% expressed Laminin 332 IHC score of 5 and 43.5% expressed IHC score of 6.

Study by Rath G et al[5] 36(64.29%) had grade 3 of them 66.67% did not express laminin 332 and 33.33% expressed laminin 332. 28.57% had MBR grade 2 of them 56.25% expressed laminin332 and 43.75% expressed laminin 332 which was not concordant with present study

Laterality of tumor association with Laminin 332 IHC score

In present study, 17(68%) had Laminin 332 IHC score of 5 and 8(32%) had IHC score of 6 in right breast whereas 15(60.0%) had Laminin 332 IHC score of 5 and 10(40%) had Laminin 332 IHC score of 6 in left breast. There was no significant difference between laterality of tumour and Laminin IHC score and limited published date was available for this parameter to compare.

Table 64:- Comparison of present study with other studies with respect to Laminin 332 IHC score and pT stage

Studies	Year	pT stage n(%)	Laminin 332 IHC score	
			Positive	Negative
Present study	2025	pT1- 6(12%)	Score 5-66.7% Score 6-33.3%	0
		pT2- 27(54%)	Score 5-66.7% Score 6-33.3%	0
		pT3- 10(20%)	Score 5-70% Score 6-30%	0
		pT4- 7(14%)	Score 5-42.9% Score 6-57.1%	0
Rath G et al[5]	2023	pT1-10(17.86%)	80%	20%
		pT2-16(28.57%)	75%	25%
		pT3-30(53.57%)	13.33%	86.67%
		pT4-0	0	0

- In present study 27(54%) of study population expressed laminin 332 out of them majority expressed laminin IHC score 5 followed by IHC score 6. 10(20%) of study population had pT3 stage among them 70% expressed laminin 332 IHC score 5 and 30% expressed IHC score of 6.

- Study done by Rath G et al[5] most of study population 30(53.57) were pT3 stage, of them 86.67% are laminin 332 negative which was not similar to present study.

Table 65:- Comparison of present study with other studies with respect to Laminin 332 IHC score and pN stage

Studies	Year	pN stage n(%)	Laminin 332 IHC Score	
			Positive	**Negative**
Present study	2025	N0 – 39(78%)	Score -5(66.7%) Score-6(33.3%)	0
		N1 – 9(18%)	Score -5(44.4%) Score-6(55.6%)	0
		N2 -0	0	0
		N3 -2(4%)	Score -5(100%) Score- 6(0)	0

- In present study 39(78%) had N0 stage out of them 5(66.7%) expressed Laminin 332 IHC score of 5 and 6(33.3%) having Laminin 332 IHC score of 6, most of them expressing IHC score of 5.
- 9(18%) had N1 stage out of them majority 55.6% expressed Laminin 332 IHC score of 6 and 44.4% expressed IHC score of 5.
- 2(4%) had N3 stage, all of them expressed Laminin 332 IHC score of 5.
- Limited published data is available on this parameter to compare.

pTNM stage association with Laminin 332 IHC score

- In present study 4(80%) and 1(20%) study population had PTNM Stage I expressed Laminin 332 IHC score 5 and 6 respectively.

- 24(64.8%) and 13(35.2%) study population had PTNM Stage II expressed Laminin 332 IHC score of 5 and 6 respectively.
    - 4(50%) and 4(50%) had PTNM Stage III expressing Laminin 332 IHC of 5 and 6 respectively.
    - Limited published data was available in English literature on this to compare.

Mean NPI association with Laminin 332 IHC score

- In present study Laminin 332 IHC score of 5 showed a significantly lower mean NPI (3.587) than those with an IHC score of 6 (3.711).
- Limited published data was available in English literature for this parameter to compare.

Table 66:- Comparison of present study with other studies with respect to Laminin 332 IHC score and LVI

Studies	Year	LVI n(%)	Laminin 332 IHC Score	
			Positive	Negative
Present study	2025	Absent- 11(22%)	Score 5 -36.4% Score 6 -63.6%	0%
		Present- 39(78%)	Score 5 -71.8% Score 6 -28.2%	0%
Rath G et al[5]	2023	Present- 36(64.29%)	8(22.22%)	28(77.78%)
		Absent- 20(35.71%)	18(90%)	2(10%)

In present study most of the study population 39(78%) LVI was present out of that 71.8% expressed Laminin 332 IHC Score 5 and 28.2% expressed laminin 332 IHC

score of 6 and LVI was absent in 11(22%) of subjects out of that 36.4% expressed IHC score of 5 and 63.6% expressed laminin IHC score of 6.

Study by Rath G et al[5] 36(64.29%) had LVI present , out of that 28(77.78%) Laminin was negative whereas 18(90%) Laminin was positive. Majority of study population were Laminin 332 IHC negative which was not in concordance with present study.

PNI association with Laminin 332 IHC score

- In present study presence of PNI 2(50%) and 2(50%) was equally distributed among IHC Scores of 5 and 6.
- PNI was absent 30(65.2%) and 16(34.8%) study population with Laminin 332 IHC Score of 5 and 6 respectively.
- Limited published data was available in English literature on this parameter to compare.

Association of TILS with Laminin 332 IHC score

In present study mean tumor-infiltrating lymphocytes score according to Laminin IHC score 6 (.4606) was more than Laminin IHC score 5(.3444). Limited published data was available in English literature on this parameter to compare.

Limitations of study

Small sample size and data was collected from single hospital, need to conduct multicentre study to assess status in a better way.

SUMMARY

SUMMARY

Triple-negative breast tumours (TNBC) are classified as aggressive variants of breast cancer, with distinct metastatic patterns and unfavourable prognosis. Laminin 332 IHC promotes the migration of breast carcinoma cells and is associated with tumour invasiveness. There were very few studies on Laminin 332 and its relation to TNBC, so that it can have potential therapeutic option in the future. In our study, we examined the expression of Laminin 332 in 50 TNBC patients.

- In present study, 56% of the study population were > 50 years of age and 44% were < 50 years, with a mean age of 50.3 years and a median age of 54.5 years.
- 52% of the study population were para 2 (P2).
- 58% of the study population were post-menopausal.
- 84% of the study population were having normal BMI.
- There was an equal distribution of tumours in both breasts (50%:50%).
- 56% of the study population were having tumour size 2-5 cm.
- 54% of the study population were having T2 stage, 20% were T3, 14% were T4 and 12% were T1 stage.
- 78% of the study population were N0 stage, 18% were N1 and 4% were N3 stage.
- 54% of the study population were having p stage 2, 16% were stage 3 and 10% were stage 1 disease.
- Infiltrating Ductal Carcinoma (IDC) 47(92%) was the most common histological type, followed by poorly differentiated IDC 2(4%) and IDC with medullary differentiation 2(4%).
- 78% of the study population showed presence of LVI and 22% LVI was absent.
- 92% study population were not showed PNI and 8% showed PNI.

- 46% of the study population showed Modified Scarf Bloom Richardson Grade III and 42% were Grade II and 12% were Grade I.
- 46% of the study population showed poor prognostic index with NPI of 3.4-5.4 and 44% showed moderate NPI of 2.4-3.4.
- 44% of study population showed high grade TILS, 32% has low grade TILS and 24% had intermediate TILS.
- 64% of study population showed laminin 332 IHC score of 5 and 36% showed IHC score of 6.
- In present study , in <55 years age group, 15 out of 22(68.2%) of the study population expressed Laminin IHC score of 5 and 7 out of 22(31.8%) expressed Laminin IHC score of 6.In >55 years age group, 17 out of 28(60.7%) of study population expressed Laminin IHC score of 5 and 11 out of 28 (39.3%) expressed Laminin IHC score of 6 with no statistical association.
- 18 out of 29 (62.1%) of postmenopausal subjects expressed Laminin 332 IHC score 5 and 11 out of 29 (37.9%) expressed Laminin 332 IHC score of 6. 14 out 21 (66.7%) of premenopausal subjects expressed Laminin 332 IHC of 5 and 7 out of 21(33.3%) expressed Laminin 332 IHC score of with no statistical association.
- 2 out of 3 (66.7%) and 1 out of 3 (33.3%) were primiparous expressed Laminin 332 IHC score 5 and 6 respectively. 18 out of 26(69.2%) and 8 out of 26 (30.8%) were para 2 expressed Laminin 332 IHC score of 5 and 6 respectively. 12 out of 21(57.1%) and 9 out of 21 (42.9%) were para 3 and above expressing Laminin 332 IHC of 5 and 6 respectively with no statistical association.
- Mean BMI of Laminin 332 IHC score 5 was 20.00 whereas Mean BMI Laminin 332 IHC score of 6 was 19.94 with no statistical association.

- 3 out of 5 (60.0%) and 2 out of 5 (40.0%) who had tumor size <2 cms expressed Laminin 332 IHC score 5 and 6 respectively. 19 out of 28(67.9%) and 9 out of 28 (32.1%) who had tumor size 2-5 cms expressed Laminin 332 IHC score of 5 and 6 respectively. 10 out of 17(58.8%) and 7 out of 17 (41.2%) who had tumor size >5cms expressing Laminin 332 IHC of 5 and 6 respectively with no statistical significance.
- 5 out of 6 (83.3%) and 1 out 6 (16.7%) study population had MSBR Grade-1 expressed Laminin 332 IHC score 5 and 6 respectively. 14 out of 21 (66.7%) and 7 out of 21(33.3%) had MSBR Grade 2 expressed Laminin 332 IHC score of 5 and 6 respectively. 13 out of 23 (56.5%) and 10 out of 23(43.5%) were Grade 3 expressing Laminin 332 IHC of 5 and 6 respectively with no statistical significance.
- 17 out of 25(68.0%) and 8 out of 25 (32%) of study population who had tumor on Left side expressed Laminin 332 IHC score 5 and Laminin 332 IHC score of 6 respectively. 15 out of 25 (60.0%) and 10 out of 25 (40%) who had tumour on Right side expressed Laminin 332 IHC of 5 and Laminin 332 IHC score of 6 respectively with no statistical significance.
- 4 out of 6(66.7%) and 2out of 6 (33.3%) who had pT1 stage expressed Laminin 332 IHC score 5 and 6 respectively. 18 out of 27(66.7%) and 9 out of 27(33.3%) fell under pT2 stage expressed Laminin 332 IHC score of 5 and 6 respectively, while 7out of 10(70.0%) and 3 out of 10 (30.0%) were pT3 stage expressing Laminin 332 IHC of 5 and 6 respectively. 3 out of 7(42.9%) and 4 out of 7(57.1%) study population had pT4 stage with no statistical significance.
- 26 out of 39 (66.7%) and 13 out of 39(33.3%) study population who had pN0 stage expressed Laminin 332 IHC score 5 and 6 respectively. 4 out of 9(44.6%) and 5 out of 9(55.6%) had pN1 stage expressed Laminin 332 IHC score of 5 and 6 respectively.

2(100%) had pN3 stage expressing Laminin 332 IHC of 5 with no statistical significance.

- 4 out of 5 (80%) and 1 out of 5(20%) study population had pTNM Stage I expressed Laminin 332 IHC score 5 and 6 respectively. 24 out of 37 (64.8%) and 13 out of 37(35.2%) had pTNM Stage II expressed Laminin 332 IHC score of 5 and 6 respectively. 4 out of 8(50%) and 4 out of 8(50%) had pTNM Stage III expressing Laminin 332 IHC of 5 and 6 respectively with no statistical significance.
- Laminin 332 IHC score of 5 showed a significantly lower mean NPI (3.587) than those with Laminin 332 IHC score of 6 (3.711) showing no statistical significance.
- Laminin 332 IHC Score 5 was more frequently related to the presence of LVI (71.8%), IHC Score 6 was associated with the absence of LVI (63.6) **with statistical significance**.
- 2 out of 4(50%) and 2 out of 4(50%) had PNI and equally distributed among IHC Scores of 5 and 6. 30 out of 46% (65.2%) and 16 out of 46(34.8%) study population PNI was absent with Laminin 332 IHC Score of 5 and 6 respectively had no statistical significance.
- In present study mean tumour-infiltrating lymphocytes score according to Laminin IHC score 6 (.4606) was more than Laminin IHC score 5(.3444) with no statistical significance.

CONCLUSION

CONCLUSION

Triple negative breast carcinomas exhibit aggressive behaviour and are associated with unfavourable clinicopathological outcomes. Laminin immunostaining may serve as a prospective prognostic marker for predicting outcomes in patients of triple-negative breast cancer. Utilizing laminin antibodies as a potent chemotherapeutic drug can facilitate effective cancer management and enhance patient survival. In this study we documented that all the TNBC patients were positive for Laminin 322, but there was statistically significant association only with LVI.

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ANNEXURE

PATIENT INFORMATION SHEET

STUDY TITLE: IMMUNOHISTOCHEMICAL EXPRESSION OF LAMININ 332 IN TRIPLE NEGATIVE BREAST CANCER : A CROSS SECTIONAL STUDY

PLACE OF STUDY: Department of Pathology, Sri Devaraj Urs Medical College, Kolar. The main aim of the study is to evaluate the role of laminin 332 expression in triple negative breast carcinomas. Your mastectomy specimen and tissue from trucut biopsy sent to the department of Pathology, SDUMC, Kolar will be used for doing this study. This study will be approved by the institutional ethical committee. The information collected will be used only for dissertation and publication purpose. In this study we are looking for expression of Laminin 332 in your specimen of triple negative breast carcinomas that was sent to dept. of pathology for diagnostic purpose analysis of Laminin 332 will help us to understand the immunohistochemical association and expression of Laminin 332 expression with age, histological type, grade and stage of triple negative breast carcinoma. There is no compulsion to agree to participate. You are requested to sign / provide thumb impression only if you voluntarily agree to participate in the study. All information collected from you will be kept confidential and will not be disclosed to any outer side.

Your identity will not be revealed. You will not receive any monitory benefits to participate in this research. This informed consent document is intended to give you a general background of study. Please read the following information carefully and discuss with your family members. You can ask Your queries related to study at any time during the study.

If you are willing to participate in the study you will be asked to sign an informed consent form by which you are acknowledging that you wish to participate in the study and entire procedure will be explained to you by the study doctor.

You are free to withdraw your consent to participate in the study any time without explanation and this will not change your future care.

All the cost incurred for collection of data, performing the immunohistochemistry tests for LAMININ 332 analysis, printing publication will be borne by the post graduate student.

For any clarification you are free to contact the investigator.

Principal Investigator: Dr Kamala. K

Mobile No: 85010380480

ರೋಗಿಯ ಮಾಹಿತಿ ಪತ್ರ

ಅಧ್ಯಯನ ಶೀರ್ಷಿಕೆ: ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ನಲ್ಲಿ ಟ್ರಿಪಲ್ ನೆಗಟಿವ್ ಲ್ಯಾಮಿನಿನ್ 332 ರ ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಕಲ್ ಅಭಿವ್ಯಕ್ತಿ : ಒಂದು ಅಡ್ಡ ವಿಭಾಗದ ಅಧ್ಯಯನ.

ಅಧ್ಯಯನದ ಸ್ಥಳ: ರೋಗಶಾಸ್ತ್ರ ವಿಭಾಗ, ಶ್ರೀ ದೇವರಾಜ ಅರಸು ವೈದ್ಯಕೀಯ ಕಾಲೇಜು, ಕೋಲಾರ.

ಸ್ತನ ಕಾರ್ಸಿನೋಮಗಳಲ್ಲಿ ಟ್ರಿಪಲ್ ನೆಗಟಿವ್ ಲ್ಯಾಮಿನಿನ್ 332 ಅಭಿವ್ಯಕ್ತಿಯ ಪಾತ್ರವನ್ನು ಮೌಲ್ಯಮಾಪನ ಮಾಡುವುದು ಅಧ್ಯಯನದ ಮುಖ್ಯ ಗುರಿಯಾಗಿದೆ. ನಿಮ್ಮ ಸ್ತನಛೇದನದ ಮಾದರಿ ಮತ್ತು ಬ್ಲಾಕ್ ಬಯಾಪ್ಸಿಯಿಂದ ಅಂಗಾಂಶವನ್ನು ರೋಗಶಾಸ್ತ್ರ ವಿಭಾಗ, ಎಸ್.ಡಿ.ಯು.ಎಂ.ಸಿ, ಕೋಲಾರಕ್ಕೆ ಕಳುಹಿಸಲಾಗಿದೆ. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ಅನುಮೋದಿಸುತ್ತದೆ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆ ಉದ್ದೇಶಕ್ಕಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಾವು ಇಲಾಖೆಗೆ ಕಳುಹಿಸಲಾದ ಸ್ತನ ಕಾರ್ಸಿನೋಮಗಳ ಟ್ರಿಪಲ್ ನೆಗಟಿವ್ ಲ್ಯಾಮಿನಿನ್ 332 ನ ಮಾದರಿ ಅಭಿವ್ಯಕ್ತಿಗಾಗಿ ಹುಡುಕುತ್ತಿದ್ದೇವೆ. ಲ್ಯಾಮಿನಿನ್ 332 ರ ರೋಗನಿರ್ಣಯದ ಉದ್ದೇಶದ ವಿಶ್ಲೇಷಣೆಗಾಗಿ ರೋಗಶಾಸ್ತ್ರವು ವಯಸ್ಸು, ಹಿಸ್ಟೋಲಾಜಿಕಲ್ ಪ್ರಕಾರ, ಗ್ರೇಡ್ ಮತ್ತು ಸ್ತನ ಕಾರ್ಸಿನೋಮದ ಟ್ರಿಪಲ್ ನೆಗಟಿವ್ ಹಂತದೊಂದಿಗೆ ಲ್ಯಾಮಿನಿನ್ 332 ಅಭಿವ್ಯಕ್ತಿಯ ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಕಲ್ ಅಸೋಸಿಯೇಷನ್ ಮತ್ತು ಅಭಿವ್ಯಕ್ತಿಯನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳಲು ನಮಗೆ ಸಹಾಯ ಮಾಡುತ್ತದೆ. ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಳ್ಳಲು ಯಾವುದೇ ಒತ್ತಾಯವಿಲ್ಲ. ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದರೆ ಮಾತ್ರ ಹೆಚ್ಚಿನ ಗುರುತನ್ನು ಸಹಿ ಮಾಡಲು / ಒದಗಿಸಲು ನಿಮ್ಮನ್ನು ವಿನಂತಿಸಲಾಗಿದೆ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಯಾವುದೇ ಮಾಹಿತಿಯನ್ನು ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ.

ನಿಮ್ಮ ಗುರುತನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಯಾವುದೇ ಮಾನಿಟರಿ ಪ್ರಯೋಜನಗಳನ್ನು ಸ್ವೀಕರಿಸುವುದಿಲ್ಲ. ಈ ತಿಳುವಳಿಕೆಯುಳ್ಳ ಸಮ್ಮತಿಯ ಕರಡನ್ನು ನಿಮಗೆ ಸಾಮಾನ್ಯ ಅಧ್ಯಯನದ ಹಿನ್ನೆಲೆಯನ್ನು ನೀಡಲು ಉದ್ದೇಶಿಸಲಾಗಿದೆ. ದಯವಿಟ್ಟು ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು

ಎಚ್ಚರಿಕೆಯಿಂದ ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ. ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದ ನಿಮ್ಮ ಪ್ರಶ್ನೆಗಳನ್ನು ನೀವು ಕೇಳಬಹುದು.

ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸಿದ್ಧರಿದ್ದರೆ, ತಿಳುವಳಿಕೆಯುಳ್ಳ ಸಮ್ಮತಿಯ ನಮೂನೆಗೆ ಸಹಿ ಹಾಕಲು ನಿಮ್ಮನ್ನು ಕೇಳಲಾಗುತ್ತದೆ ಮತ್ತು ಅದರ ಮೂಲಕ ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಬಯಸುತ್ತೀರಿ ಎಂದು ಒಪ್ಪಿಕೊಳ್ಳುತ್ತೀರಿ ಮತ್ತು ಸಂಪೂರ್ಣ ಕಾರ್ಯವಿಧಾನವನ್ನು ಅಧ್ಯಯನ ವೈದ್ಯರು ನಿಮಗೆ ವಿವರಿಸುತ್ತಾರೆ.

ವಿವರಣೆಯಿಲ್ಲದೆ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಿಮ್ಮ ಒಪ್ಪಿಗೆಯನ್ನು ಹಿಂಪಡೆಯಲು ನೀವು ಸ್ವತಂತ್ರರಾಗಿದ್ದೀರಿ ಮತ್ತು ಇದು ನಿಮ್ಮ ಭವಿಷ್ಯದ ಕಾಳಜಿಯನ್ನು ಬದಲಾಯಿಸುವುದಿಲ್ಲ.

ಡೇಟಾ ಸಂಗ್ರಹಣೆ, ಲ್ಯಾಮಿನಿನ್ 332 ವಿಶ್ಲೇಷಣೆಗಾಗಿ ಇಮ್ಯುನೊಹಿಸ್ಟೊಕೆಮಿಸ್ಟ್ರಿ ಪರೀಕ್ಷೆಗಳನ್ನು ನಡೆಸುವುದು, ಮುದ್ರಣ ಪ್ರಕಟಣೆಗೆ ತಗಲುವ ಎಲ್ಲಾ ವೆಚ್ಚವನ್ನು ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿಯು ಭರಿಸಬೇಕಾಗುತ್ತದೆ.

ಯಾವುದೇ ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ತನಿಖಾಧಿಕಾರಿಯನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ.

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿ: ಡಾ|| ಕಮಲಾ ಕೆ

ದೂರವಾಣಿ ಸಂಖ್ಯೆ: 8501038048

INFORMED CONSENT FORM

STUDY TITLE: IMMUNOHISTOCHEMICAL EXPRESSION OF LAMININ 332 IN TRIPLE NEGATIVE BREAST CANCER : A CROSS SECTIONAL STUDY

I, _____have read or have been read to me the patient information sheet and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information will be collected and disclosed during the study.

I have had my opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction.

I, the undersigned, agree to participate in this study and authorize the collection and disclosure of my personal information for the dissertation.

Name and signature / thumb impression Date:

(subject) Place:

Name and signature / thumb impression Date:

(Witness/Parent/ Guardian/ Husband) Place:

ಒಪ್ಪಿಗೆ ಪತ್ರ

ಶೀರ್ಷಿಕೆ: ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ನಲ್ಲಿ ಟ್ರಿಪಲ್ ನೆಗೆಟಿವ್ ಲ್ಯಾಮಿನಿನ್ 332 ರ ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಕಲ್ ಅಭಿವ್ಯಕ್ತಿ :

ಒಂದು ಅಡ್ಡ ವಿಭಾಗದ ಅಧ್ಯಯನ

ನಾನು ಮಾಹಿತಿ ಹಾಳೆಯನ್ನು ಓದಿದ್ದೇನೆ ಅಥವಾ ನನಗೆ ಓದಿ ತಿಳಿಸಿದ್ದಾರೆ ಮತ್ತು ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಬಳಸಲಾಗುವ ವಿಧಾನ, ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಗೆ ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಪ್ರಯೋಜನಗಳು ಮತ್ತು ಮಾಹಿತಿಯ ಸ್ವರೂಪವನ್ನು ಸಂಗ್ರಹಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಬಹಿರಂಗಪಡಿಸಲಾಗುತ್ತದೆ. ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳಿಗೆ ಸಂಬಂಧಿಸಿದಂತೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನ್ನ ಅವಕಾಶವನ್ನು ನಾನು ಹೊಂದಿದ್ದೇನೆ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ.

ಈ ಕೆಳಗೆ ಸಹಿಮಾಡಿರುವ ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿರುತ್ತೇನೆ ಮತ್ತು ಕಾಗದದ ಪ್ರಸ್ತುತಿಗಾಗಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯನ್ನು ಅಧಿಕೃತಗೊಳಿಸುತ್ತೇನೆ.

ಹೆಸರು ಮತ್ತು ಸಹಿ / ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

(ವಿಷಯ)

ಹೆಸರು ಮತ್ತು ಸಹಿ / ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

(ಸಾಕ್ಷಿ/ಪೋಷಕ/ಗುರು/ಪತಿ)

ಮತ್ತಷ್ಟು ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ಅಧ್ಯಯನಶೋಧಕವನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು

ಡಾ|| ಕಮಲ.ಕೆ

Name:	
Age:	Hospital Number:

PATIENT PROFORMA

Anonymised Sample No:

Chief complaint:

History of presenting illness:

Past history:

Personal history:

Menopausal state:

Premenopausal/Postmenopausal

BMI:

Normal/overweight/obese/severe obesity/morbid obesity/super obesity

Local examination:

Biopsy Number:

Gross:

Tumor size:

Microscopy:

Tumor grade:

Lymphovasclar invasion:

Tumor Infiltrating lymphocytes :

NPI:

Histopathological diagnosis:

Grading:

Immunohistochemical scoring:

Estrogen Receptor :

Progesterone Receptor:

Her 2 neu:

Ki 67:

Laminin 332:

KEY TO MASTER CHART

P – Parity

L- living

BMI – Basal metabolic index

T – T staging according to 8th TNM Staging of breast carcinoma

N – N staging according to 8th TNM Staging of breast carcinoma

M – M staging according to 8th TNM Staging of breast carcinoma

ER – Estrogen Receptor protein

PR -Progesterone Receptor protein

Her2 neu – Human Epidermal Growth Factor Receptor 2 neu protein

NPI – Nottingham Prognostic Index

TN – Triple negative

MASTER CHART

S.NO	HOSPITAL NUMBER	BIOPSY NUMBER	AGE	SEX	PARITY	MENOPAUSAL STATUS	BMI	LATERALITY OF TUMOUR	SPECIMEN TYPE	TUMOR SIZE	MODIFIED BLOOM RICHARDSON GRADE	NPI	pT STAGE	pN STAGE	pM STAGING	pTNM STAGE	STAGE	HISTOPATHOLOGICAL DIAGNOSIS	TUMOR INFILTRATING LYMPHOCYTES	LVI	PNI	ESTROGEN RECEPTOR	PROGESTERONE RECEPTOR	HER2NEU	IHC SCORE LAMININ 332	IHC LAMININ 332 FINAL GRADE	
1	626421	B-2334-18	61Y	FEMALE	P2L2	POSTMENOPAUSAL	18	LEFT BREAST	MASTECTOMY	7.5X7X7.4CM	GRADE-II	3	T4A	N1	MX	T4aN1MX	IIIB	INFILTRATING DUCTAL CARCINOMA	8%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
2	647618	B-2732B-18	39Y	FEMALE	P2L2	PREMENOPAUSAL	17	LEFT BREAST	MASTECTOMY	6X3X3 CM	GRADE-II	2.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	75%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
3	652105	2831A6-18	48Y	FEMALE	P3L3	POST MENOPUSAL	19	RIGHT BREAST	MASTECTOMY	6.8X6X3CM	GRADE-II	3.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	5%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
4	651100	B-1972E-18	28Y	FEMALE	P2L2	PREMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	3.8X3X2CM	GRADE-I	2.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	8%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
5	647618	B-2372-E	36Y	FEMALE	P1L1	PREMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	6X5X3CM	GRADE-III	3.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	60%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
6	786531	B-2830-F	43Y	FEMALE	P2L2	PREMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	3X2.2X2.5CM	GRADE-III	5	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	65%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
7	740192	2390R-19	75Y	FEMALE	P2L2	POSTMENOPAUSAL	22	LEFT BREAST	MASTECTOMY	3X2.7X3CM	GRADE-II	3.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	70%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
8	746923	B-347J-19	65Y	FEMALE	P3L3	POST MENOPUSAL	19	RIGHT BREAST	MASTECTOMY	7X6.5X5.5CM	GRADE-II	3.4	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	6%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
9	740099	B-1410F-19	55Y	FEMALE	P2L2	POSTMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	3.5X3X3CM	GRADE-III	4.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	70%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
10	351831	B644H-24	45Y	FEMALE	P4L4	PREMENOPAUSAL	25	LEFT BREAST	MASTECTOMY	3.3X2X1.8CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	10%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
11	742231	B371G-19	57Y	FEMALE	P3L2	POSTMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	2.5X3X2CM	GRADE-II	3.4	T2	N3	MX	T2N3MX	IIIC	INFILTRATING DUCTAL CARCINOMA	6%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
12	786531	B2472E-19	60Y	FEMALE	P5L5	POSTMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	6X4X3CM	GRADE-III	5.2	T4	N1	MX	T4N1MX	IIIB	INFILTRATING DUCTAL CARCINOMA	70%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
13	582951	B-977H-23	67Y	FEMALE	P2L2	POSTMENOPAUSAL	19	LEFT BREAST	MASTECTOMY	5X4X1.5CM	GRADE-III	4.8	T4	N1	MX	T4N1MX	IIIB	INFILTRATING DUCTAL CARCINOMA	90%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
14	746844	B-2549K-19	45Y	FEMALE	P3L3	PREMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	3X2X2CM	GRADE-III	4.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	60%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
15	702038	B-1108G-19	40Y	FEMALE	P2L2	PREMENOPAUSAL	18	LEFT BREAST	MASTECTOMY	3X2.5X1.5CM	GRADE-II	3	T2	N0	MX	T2N0MX	IIA	DIFFERENTIATED INFILTRATING DUCTAL CA	5%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
16	734962	B-369H-19	58Y	FEMALE	P3L3	POSTMENOPAUSAL	17	LEFT BREAST	MASTECTOMY	2.5X1.5X1CM	GRADE-II	3.2	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	6%-LOW	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
17	845622	B-228G-20	71Y	FEMALE	P4L4	POSTMENOPAUSAL	16	LEFT BREAST	MASTECTOMY	2.8X2X1.5CM	GRADE-I	2.9	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	0%-INTERMEDIAT	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
18	865603	B-1462D-20	75Y	FEMALE	P3L3	POSTMENOPAUSAL	18	LEFT BREAST	MASTECTOMY	1.3X1.1X0.9CM	GRADE-II	3.4	T1	N0	MX	T1N0MX	IA	INFILTRATING DUCTAL CARCINOMA	8%-LOW	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
19	820441	B-2372F-20	45Y	FEMALE	P2L2	PREMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	1.5X1.2X1CM	GRADE-II	3.3	T1	N0	MX	T1N0MX	IA	INFILTRATING DUCTAL CARCINOMA	8%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
20	820441	B-910D-20	51Y	FEMALE	P3L3	POSTMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	1.5X1.5X1CM	GRADE-II	3.1	T1	N0	MX	T1N0MX	IA	INFILTRATING DUCTAL CARCINOMA	0%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
21	815423	B-1878G-20	65Y	FEMALE	P2L2	POSTMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	5.5X5X4CM	GRADE-I	2.9	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	6%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
22	61507	B-1697H-21	42Y	FEMALE	P1L1	PREMENOPAUSAL	21	LEFT BREAST	MASTECTOMY	2X2X1CM	GRADE-II	3.3	T1	N0	MX	T1N0MX	IA	INFILTRATING DUCTAL CARCINOMA	5%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
23	87734	B-1858E-21	57Y	FEMALE	P3L3	POSTMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	4X3X2.5CM	GRADE-II	3.6	T2	N0	MX	T2N0MX	IIA	DUCTAL CARCINOMA WITH MEDULLARY DIF	55%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
24	62864	B-1923H-21	52Y	FEMALE	P2L2	POSTMENOPAUSAL	25	RIGHT BREAST	MASTECTOMY	3X2.5X2.5CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	60%-HIGH	SEEN	SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
25	62541	B-2059D-21	60Y	FEMALE	P2L2	POSTMENOPAUSAL	21	LEFT BREAST	MASTECTOMY	3X2X1CM	GRADE-III	4.2	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	0%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
26	55208	B-2155E-21	58Y	FEMALE	P3L3	POSTMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	3X2X1.5CM	GRADE-III	4.4	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	55%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
27	63619	B-2278H-21	64Y	FEMALE	P2L2	POSTMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	6.2X4X3CM	GRADE-II	3.1	T4	N1	MX	T4N1MX	IIIB	DUCTAL CARCINOMA WITH MEDULLARY DIF	7%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
28	63366	B-41G-22	56Y	FEMALE	P2L2	POSTMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	1.5X1.5X1CM	GRADE-II	3.1	T1	N0	MX	T1N0MX	IA	INFILTRATING DUCTAL CARCINOMA	6%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
29	66662	B-165H-22	68Y	FEMALE	P3L3	POSTMENOPAUSAL	17	LEFT BREAST	MASTECTOMY	5.4X4.5X4CM	GRADE-I	2.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	5%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
30	410060	B-2198K-24	47Y	FEMALE	P2L2	PREMENOPAUSAL	18	LEFT BREAST	MASTECTOMY	4.3X2.2X2CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	80%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
31	885577	B-1472M-22	39Y	FEMALE	P2L2	PREMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	7X6.3X5.4CM	GRADE-III	4.4	T4	N3	MX	T4N3MX	IIIC	INFILTRATING DUCTAL CARCINOMA	70%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
32	903629	B-1817K-22	70Y	FEMALE	P2L2	POSTMENOPAUSAL	22	LEFT BREAST	MASTECTOMY	3X2.2X1.8CM	GRADE-III	4.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	70%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
33	63366	B-1167D-22	41Y	FEMALE	P2L2	PREMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	3.4X2.2X1.2CM	GRADE-II	3	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	65%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
34	69625	B-645E-22	49Y	FEMALE	P4L4	PREMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	6.2X4.2X3CM	GRADE-II	3.8	T4	N1	MX	T4N1MX	IIIB	INFILTRATING DUCTAL CARCINOMA	5%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
35	134877	B-2499E-22	56Y	FEMALE	P2L2	POSTMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	2.6X1.4X1CM	GRADE-I	2.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	72%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
36	144626	B-2975G-22	45Y	FEMALE	P3L3	PREMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	3.4X2.2X1.2CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	65%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
37	71915	B-717H-22	45Y	FEMALE	P2L2	PREMENOPAUSAL	25	RIGHT BREAST	MASTECTOMY	2.6X1.4X1CM	GRADE-I	2.9	T2	N1	MX	T2N1MX	IIB	INFILTRATING DUCTAL CARCINOMA	75%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
38	240102	B-1971K-23	41Y	FEMALE	P3L3	PREMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	3.4X2.2X1.2CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	5%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
39	228810	B-2573G-23	43Y	FEMALE	P2L2	PREMENOPAUSAL	21	RIGHT BREAST	MASTECTOMY	3.2X2.3X1.3	GRADE-III	4	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	0%-INTERMEDIAT	NOT SEEN	SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
40	229831	B-1721K-23	40Y	FEMALE	P3L3	PREMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	5.5X4.5X4CM	GRADE-III	4.4	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	77%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
41	92482	B-272J-23	61Y	FEMALE	P2L2	POSTMENOPAUSAL	21	LEFT BREAST	MASTECTOMY	1.5X1X1.1CM	GRADE-III	3.8	T1	N1	MX	T1N1MX	IIA	INFILTRATING DUCTAL CARCINOMA	68%-HIGH	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
42	190871	B-306E-23	65Y	FEMALE	P4L4	POSTMENOPAUSAL	25	RIGHT BREAST	MASTECTOMY	5.6X4X3.1CM	GRADE-II	2.8	T4	N1	MX	T4N1MX	IIIB	Y DIFFERENTIATED INVASIVE BREAST CARCI	0%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
43	227598	B-1633K-23	54Y	FEMALE	P2L2	POSTMENOPAUSAL	21	LEFT BREAST	MASTECTOMY	3X2.2X1.8CM	GRADE-III	3.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	4%-LOW	SEEN	SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
44	251719	B-2210J-23	60Y	FEMALE	P3L3	POSTMENOPAUSAL	20	LEFT BREAST	MASTECTOMY	2.6X1.4X1CM	GRADE-III	4.8	T2	N1	MX	T2N1MX	IIB	INFILTRATING DUCTAL CARCINOMA	6%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
45	274944	B-3121H-23	59Y	FEMALE	P1L1	POSTMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	6X2.2X2CM	GRADE-III	3.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	0%-INTERMEDIAT	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
46	573137	B-648J-23	50Y	FEMALE	P2L2	PREMENOPAUSAL	18	RIGHT BREAST	MASTECTOMY	2.6X1.4X1CM	GRADE-III	3.8	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	5%-INTERMEDIAT	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
47	372348	B-1366J-24	60Y	FEMALE	P3L3	POSTMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	6X5X4CM	GRADE-II	2.8	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	80%-HIGH	SEEN	SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
48	374326	B-1483K-24	46Y	FEMALE	P2L2	PREMENOPAUSAL	21	LEFT BREAST	MASTECTOMY	4.3X2.2X2CM	GRADE-III	3.6	T2	N0	MX	T2N0MX	IIA	INFILTRATING DUCTAL CARCINOMA	85%-HIGH	NOT SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	
49	381395	B-1601J-24	44Y	FEMALE	P3L3	PREMENOPAUSAL	22	RIGHT BREAST	MASTECTOMY	6.5X3X2.5CM	GRADE-II	4	T3	N0	MX	T3N0MX	IIB	INFILTRATING DUCTAL CARCINOMA	5%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	5	GRADE-2	
50	394664	B-1807K-24	64Y	FEMALE	P2L2	POSTMENOPAUSAL	20	RIGHT BREAST	MASTECTOMY	3X2X1CM	GRADE-II	2.6	T2	N0	MX	T2N0MX	IIA	INFINTRATING DUCTAL CARCINOMA	5%-LOW	SEEN	NOT SEEN	NEGATIVE	NEGATIVE	NEGATIVE	6	GRADE-2	