RESEARCH ARTICLE

Decreased Expression of *CD247* and *CD4* Immune Marker Predicts Poor Prognosis in Triple Negative Breast Cancer

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Abstract

Objective: Triple negative breast cancer (TNBC) is an aggressive from of breast cancer and is associated with poor prognosis. Tumor microenvironment of breast cancer consists of a wide   range of cell types, including tumor-infiltrating lymphocytes (TILs). Accumulating evidence indicate that TILs play a crucial role in cancer progression and resistance to standard chemotherapy. **Method:** We used online computational tools to evaluate the prognostic significance of *CD247* and *CD4* in TNBC. **Results:** TNBC patients with lower expression of *CD247* and *CD4* have much shorter relapse- free survival and overall survival than the patients with higher expression of these genes. *CD247* and *CD4* expression show a strong positive correlation with tumor-infiltrating dendritic cells, B-cells, *CD4+*, *CD8+,* and neutrophils. **Conclusion:** We've concluded that low levels of *CD247* and *CD4* may stop immune cells from entering the area around the tumor, which stops cancer cells from being killed and gives the patient a bad outlook. These findings suggest that *CD247* and *CD4* may be useful biomarkers or as a target to understand the progression of TNBC. Our findings also suggest that *CD247* and *CD4* targeted therapeutics should be explored in detail, and could be a potentially used as atreatment strategy for TNBC.

Keywords: Breast Cancer- Triple-negative breast cancer- tumor-infiltrating lymphocytes- tumor microenvironment

Introduction

Breast cancer is the foremost cause of cancer-related deaths in women worldwide [1]. In 2020, 2.3 million women were diagnosed, and 685,000 died due to breast cancer [2]. In the United States alone, 271,270 new cases of breast cancer were reported in 2019, with 42,260 fatalities [3]. It is predicted that by the year 2030 the global annual incidence of breast cancer will rise to 3.2 million [4]. Based on the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (*HER2*), and *Ki-67*, breast carcinoma is characterized into four distinct molecular subtypes [5]. Luminal A subtype, having ER+, PR+, *HER2-*, and low expression of *Ki-67*, comprises 40% of breast cancers [6]. Luminal B subtype, ER+, PR+, *HER2*+/-, and high expression of *Ki-67*, whereas, *HER2* positive (*HER2*+) subtype, is hormone receptor negative (ER and/or PR negative) and *HER2*+. Lastly, triple-negative breast cancers (TNBC) subtype is negative for ER, PR and *HER2* [7]. The receptor status and subtypes also have implication on tumor aggression and response therapy.

About 10-15% of breast cancer are TNBC, and have poor prognosis and high recurrence rates [8]. TNBCs tumors are heterogeneous, biologically more aggressive and are generally larger in size [9]. TNBC patients are usually younger than the patients with other subtypes types of breast cancer. In patients with TNBC the expression of *Ki-67* is significantly high and associated with lymph node metastasis [10]. Due to their aggressive characteristics and lack of targeted therapies, TNBCs still remains a major clinical challenge [11]. Chemotherapy is used to treat primary and metastatic diseases, and targeted therapies, including immunotherapy, are emerging treatment modalities for TNBCs [12]. TNBCs are a broad group of malignancies that are further classified into six different subtypes based on their molecular heterogeneity and the gene expression profile, basal-like subtypes (BL 1 and BL2), immunomodulatory (IM), mesenchymal, mesenchymal stem-like and luminal androgen receptor subtype. Previous studies have shown that the basal-like subtype of TNBC have downregulation of T-cells, B-cells

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and natural killer cells which is associated with worse prognosis of the patients [13].

CD247, also known as T-cell antigen receptor (TCR)-Z, or CD3 Zeta-chain, is a 16-kDa molecule that is a key component of the TCR complex. CD3 zeta chain plays an essential role in the activation of the antigenic peptides that are presented by the human leukocyte antigen on antigen-presenting cells [14]. The downregulation of *CD247* often correlates with reduced expression of other T-cell-associated signal-transducing molecules like ZAP-70 and p56lck [15], decreased calcium flux [16] and T-cell clearance. Tumor-infiltrating lymphocytes (TILs) have been linked to better outcomes for women with breast cancer [17]. Several Investigations demonstrated that innate immune cells (neutrophils, macrophages, dendritic cells, innate lymphocytes, NK cells, and myeloid inhibitory cells) and adaptive immune cells (T cells and B cells) contribute to tumor progression when present in the tumor microenvironment. Higher *CD4+* T cell infiltration in tumors is associated with better overall survival and reduced recurrence rates in early-stage breast cancer [18]. Thus, the tumor microenvironment is a barrier to effector immune cells and reduces the effectiveness of NK cells and adaptive T cells [19]. The decreased expression of *CD247* is associated with changed T-cell responsiveness and proliferation capacity [20]. Reduced levels of *CD247* in TILs and peripheral blood cells are correlated with a number of cancers, including gastric carcinoma, head and neck cancer, and bladder cancer [21].

The Insilco analysis of publicly available data from The Cancer Genome Atlas (TCGA) is an unbiased approach that can predict outcome when applied to appropriately selected cohorts and adapt to analyze the involvement of genes in cancer progression. We combined multi-perspective databases to analyze the prognostic role of *CD247* and *CD4* genes and their association with TILs with special emphasis on the TNBC subtype.

Materials and Methods

Kaplan–Meier Survival Analysis

The KM Plotter accessible at http://kmplot.com/analysis/, is an online database containing microarray gene expression data and survival data generated from the Gene Expression Omnibus and the TCGA [22]. This approach has been widely used to assess the impact of gene on the rate of survival across more than 20 distinct cancer types [23]. We used this database to investigate the relationship between gene-specific mRNA expression with relapse-free survival (RFS) and overall survival (OS) of breast cancer, and intrinsic subtypes of breast cancer. We also assessed RFS in Pietenpol subtypes of TNBC with respect to the clinical stage. The investigation was restricted on the breast cancer subtypes of 2277 luminal A patients, 1451 luminal B patients, 846 basal type patients, and 315 Her-2 patients [24].

Gene Expression Analysis using UALCAN Database

UALCAN is used to analyze gene expression and to evaluate promoter DNA methylation from the TCGA data of various types of cancer [25]. It was used to analyze gene expression of *CD4* and *CD247* in breast tumors and normal tissues. Using TCGA transcriptome and clinical patient data, UALCAN enables researchers to study the expression level of genes, not only to compare primary tumor with normal tissue samples, but also to compare across different tumor subgroups as defined by pathological cancer stage, tumor grade, and other clinic-pathologic features [25].

c-Bioportal for Cancer Genomics

The c-BioPortal is a repository of multidimensional cancer genomics data sets, with data from over 5,000 tumor samples from 20 different types of cancer [26]. Mutation analysis of genes of tumor-infiltrating immune markers such as *CD247, CD8, CD3D, PDCD1, CD3E, MS4A2,* and *CD3E* was performed by applying this tool to the publicly available whole exome sequencing data of breast cancer patients. The Oncoprints were obtained from cBioportal upon querying the database specifically for the copy number alterations of selected genes in the samples from the analyzed tumor types.

Analysis of Tumor Immunological Features of TIL Using TIMER

The TIMER is an online computational tool for the evaluation of tumor immune cells in the publicly available TCGA database [27]. TIMER database consists of 10879 samples of 32 cancer types from the TCGA database to evaluate immune infiltrate abundance. TIMER2.0 also provides an 'estimation component' to infer immune infiltrates on user-provided expression profiles using multiple algorithms association between immune infiltrates and gene expression. These estimated tumor immune infiltrate populations have been associated with genomic and transcriptomic changes in the tumors, providing insight into tumor-immune interactions [28]. The association between the expression of *CD247* and *CD4* genes with TILs in breast cancer with tumor-infiltrating immune cells (B cells, *CD4+* T cells, CD8+ cells, macrophages, neutrophils and dendritic cells), were selected for correlation by TIMER. Tumor purity was taken into consideration when calculating the Spearman's correlation. P-value of < 0.05 was considered statistically significant [29].

Results

CD247 and CD4 lower expression leads to poor survival in Breast cancer patients

Tumor-infiltrating lymphocytes play a crucial role in tumor growth and progression of a variety of cancers [30]. To determine the prognostic value of *CD247* and *CD4* in BC, Kaplan-Meier survival curves were plotted (Figure 1). The mRNA expression of *CD247* was significantly correlated with OS and RFS of breast cancer patients in GEO, EGA and TCGA databases (Figure 1, A and B). According to the survival analyses, the upper quartile survival of breast cancer patients with lower expression of *CD247* in RFS was 41.04 months as compared to 61 months with higher expression cohort. We also compared the upper quartile survival in OS of BC.
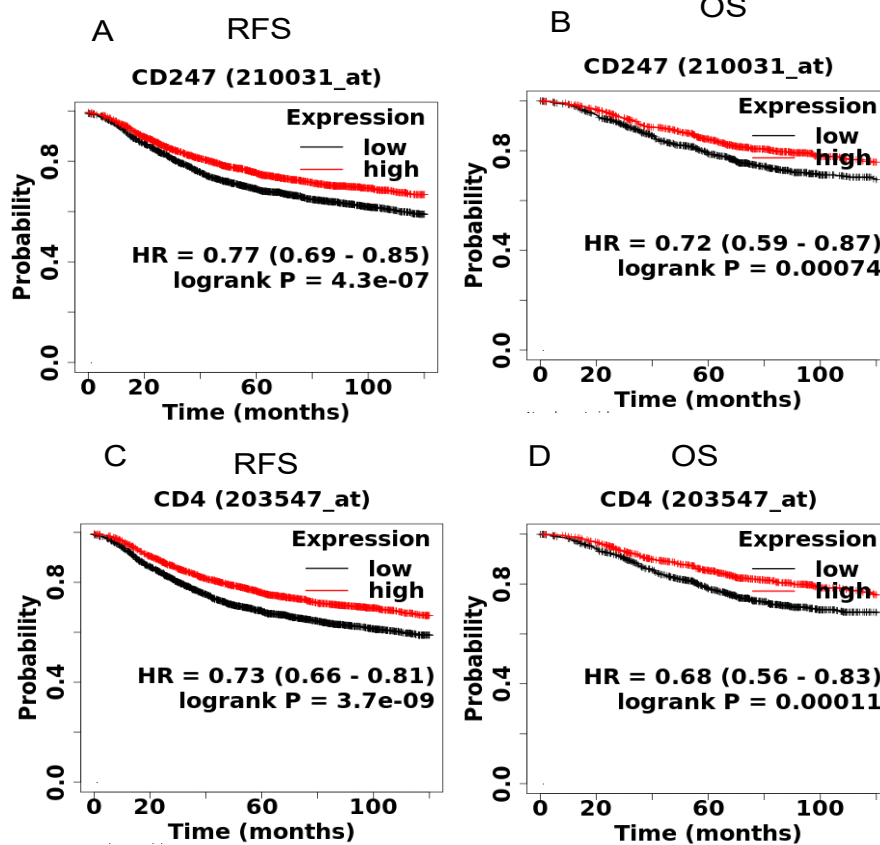
Figure 1. Prognostic Value of *CD247* and *CD4* T-cell markers in Breast Cancer. Kaplan-Meier survival curves were plotted from the publicly available KM plotter database. RFS (A) and OS (B) analysis of *CD247* in breast cancer. RFS (C) and OS (D) of *CD4* expression in breast cancer.

Survival analysis showed that the low expression cohort, the upper quartile survival was 74.07 as compared to 138 months in the high expression cohort (Table 1).

The prognostic value of *CD4* was significantly correlated to OS and RFS (Figure 1, C and D). Analysis showed that the upper quartile survival of breast cancer patients with lower expression of *CD4* in RFS is 40.34 months as compared to 62.7 months with high expression. In OS the upper quartile survival in low expression cohort was 69.99 months as compared to 135.88 months with high expression cohort.

The Prognostic value of CD247 and CD4 is associated with luminal B and Basal subtype of BC

Next, we determined the prognostic value of *CD247* in different intrinsic subtype, pathological grade and lymph node status of breast cancer (Figure 2). *CD247* showed a high predictive value in basal and luminal B subtypes of BC (Figure 2, B and D). In the basal subtype of BC, the upper quartile RFS in low expression of *CD247* was

16.6 months as compared to 38 months in high expression cohort. In luminal B the upper quartile survival was 146.5 months in the low expression cohort and 228.85 months in high expression cohort (Table 2).

Further, interestingly, *CD4* also showed the high prognostic values in luminal B and basal subtypes of BC. The upper quartile survival of luminal B subtype with lower expression of *CD4* in RFS is 146.5 months as compared to 171.43 months within high expression cohort (Figure 3). In case of basal subtype, the upper quartile survival in the low expression cohort was 15.28 months as compared to 44.22 months with high expression cohort. There was a three-fold difference in the RFS period between the *CD4* low expression cohort vs. the high expression cohort in the basal subtype of breast cancer (Table 2).

After obtaining the prominent prognostic values of *CD247* and *CD4* in basal subtypes of breast cancer, we further determined the prognostic values of *CD247* among Pietenpol subtypes of TNBC. Pietenpol subtypes

Table 1. Correlation between mRNA Expression of *CD247* and *CD4* with Relapse Free Survival and Overall Survival in Breast Cancer.

Genes	Survival	P-value	HR	CI	Low expression cohort (months)	High expression Cohort (months)
CD247 210031_at	RFS	7.70E-07	0.77	0.7-0.86	41.04	61
	OS	0.00059	0.72	0.59-0.87	74.07	138
CD4 203547_at	RFS	3.10E-09	0.74	0.67-0.82	40.34	62.7
	OS	0.00025	0.7	0.58-0.85	69.99	135.88

Table 2. Correlation between mRNA Expression of *CD247* and *CD4* with Relapse Free Survival in Different Intrinsic Subtypes of Breast Cancer

Gene	Intrinsic Subtype	No. of patients	Hazard Ratio	P value	RFS (in Months)	
					Low expression Cohort	High expression Cohort
	Luminal A	4929	0.89	0.15	216.66	228.85
CD247	Luminal B	1491	0.68	2.40E-05	146.5	171.43
	HER2+	315	0.55	0.0011	17	25.76
	Basal	846	0.61	1.30E-05	16.6	38
	Luminal A	2277	0.087	0.082	73	90
CD4	Luminal B	1491	0.72	0.0002	146.5	171.43
	HER2+	315	0.56	0.0014	16.3	37
	Basal	846	0.051	6.70E-09	15.28	44.22

is the molecular classification of TNBC subtypes into six categories i.e BL 1 and BL2, immunomodulatory (IM), mesenchymal, mesenchymal stem-like and luminal androgen receptor subtype [9]. Despite having low sample size, luminal androgen receptor showed a significant association of *CD247* expression with RFS (Figure 4 F). In *CD4*, basal like-1, Mesenchymal and luminal androgen receptor subtype showed a significant association with RFS (Figure 5A, D and F). Among the Peitenpol subtype of TNBC, there was a five-fold differencein the survival period (RFS) between the *CD4* low expression cohorts vs. high expression cohort in the basal-like 1 subtype of TNBC (Table 3).

Expression of CD4 and CD247 in primary breast cancer is decreased

Once we found that *CD247* and *CD4* expression are associated with the survival outcome of breast cancer patients, we wanted to further characterize the expression of these genes in primary tumor and normal tissue. To investigate the expression of *CD247* and *CD4* in breast cancer, we performed a group analysis of clinical pathological features of BC in OncoDB database. Analysis showed that the mRNA levels of *CD247* and *CD4* were significantly higher in normal tissue than in tumor tissue (Figure 6A and B). Further, the gene expression was analyzed by UALCAN database. Interestingly; UALCAN
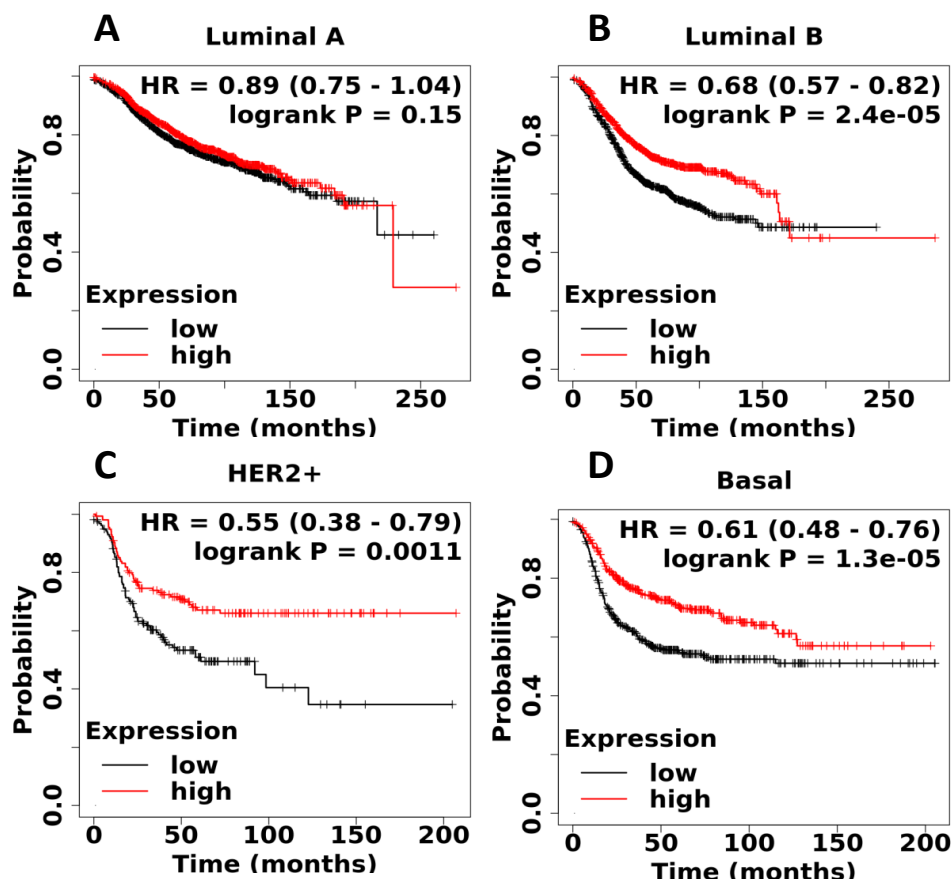

Figure 2. Low Expression of *CD247* is Significantly associated with Relapse Free Survival (RFS) of Patients with Luminal B and Basal Like Breast Cancer. (A-D), Kaplan-Meier survival curves (RFS) plotted for intrinsic subtypes of BC.
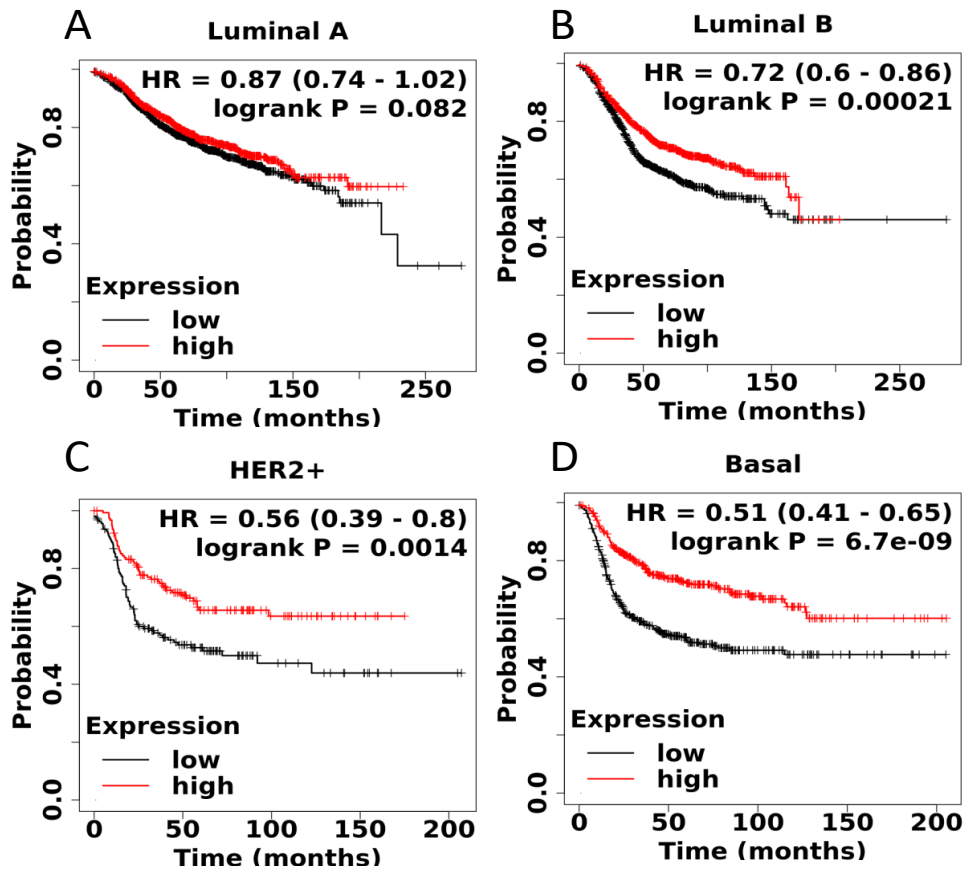
Figure 3. Low Expression of *CD4* is Significantly associated with Relapse Free Survival (RFS) of Patients with Luminal B, Basal like and HER2+ subtype Breast Cancer. (A-D), Kaplan-Meier survival curves (RFS) plotted for intrinsic subtypes of BC.
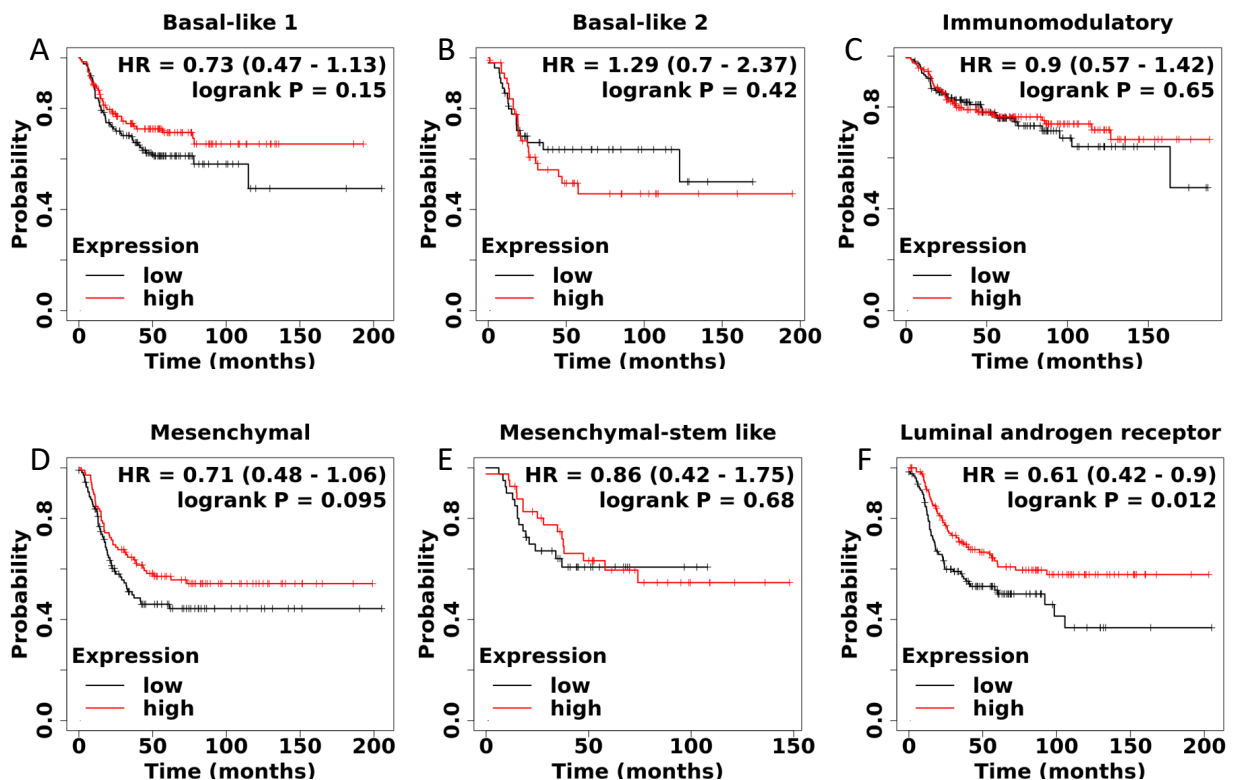

Figure 4. Prognostic Role of mRNA Expression of *CD247*, A (n=251), B (n=101), C (n=300), D (211), E(n=81), and F (n=253) with Relapse Free Survival (RFS) in Pietenpol Subtypes of Triple Negative Breast Cancer (TNBC).
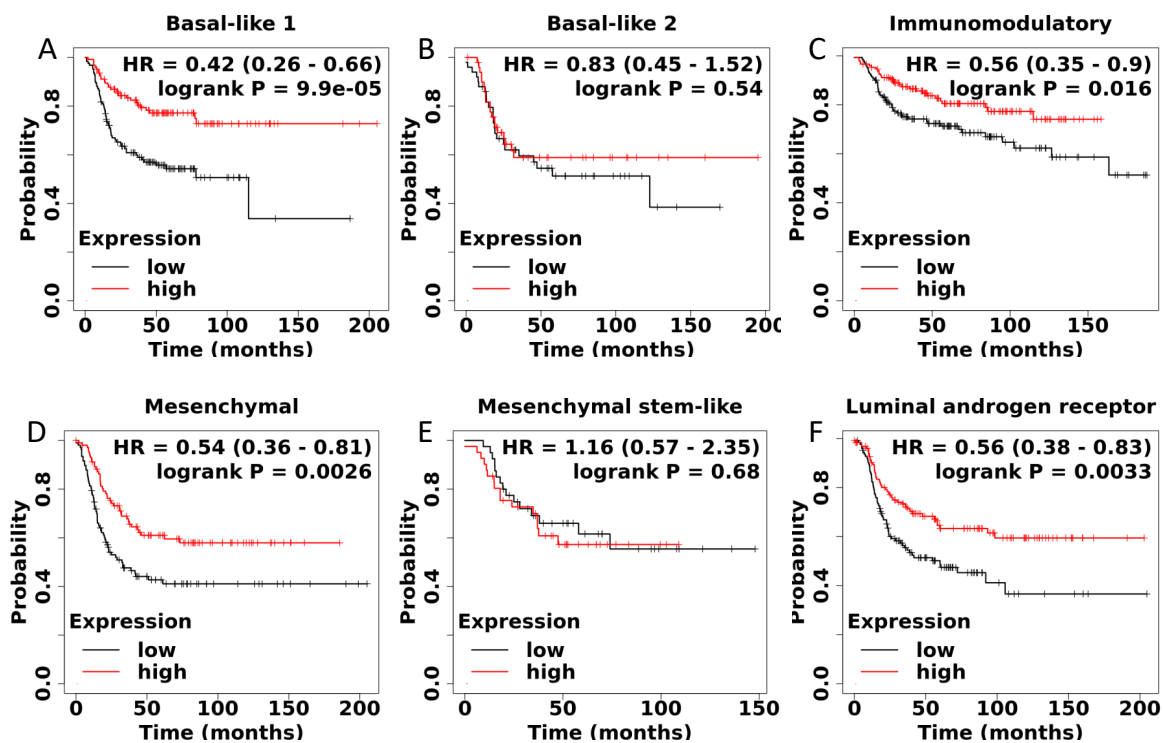
Figure 5. Prognostic Role of mRNA Expression of *CD4*, A (n=251), B (n=101), C (n=300), D (211), E (n=81), and F (n=253) with Relapse Free Survival (RFS) in Pietenpol Subtypes of Triple Negative Breast Cancer (TNBC).

data also suggested that the expression levels of *CD247* and *CD4* were higher in normal tissue as compared to the tumor tissue (Figure 6C and D). Thus, OncoDB data is consistent with data derived fromUALCAN database with respect to *CD4* and *CD247* data base.

Somatic mutations in CD247 and CD4 genes were uncommon

The c-BioPortal was used to analyze the somatic mutations in the gene *CD247* and *CD4* in patients with breast cancer. To explore the contribution of genetic alterations, mutation analysis of tumor-infiltrating

immune markers such as *CD247*, *CD8, CD3D, PDCD1, CD3E, MS4A2*, and *CD3E* was performed by applying the cBioPortal (www.cbioportal.com) tool to the publicly available whole exome sequencing data of breast cancer patients. Among these genes, *CD247* and *CD4* genes were highly mutated in 21% and 2.6%, respectively (Figure 7) respectively, whereas other genes were mutated in less than 1.0%, in patients with breast cancer, where most of these alterations were due to the gene amplification.

Expression of CD247 and CD4 correlates with TILs BC

The role of *CD247* and *CD4* in the regulation of

Table 3. Correlation between mRNA Expression of *CD247* and *CD4* with Relapse Free Survival (RFS) in Pietenpol Subtypes of Triple Negative Breast Cancer.

| Gene	TNBC Subtype	No. of patients	Hazard Ratio	P value	RFS (in Months)	
					Low expression Cohort	High expression Cohort
	Basal-like(BL1)	251	0.73	0.15	18.35	29
CD247	Basal Like (BL2)	101	1.29	0.4	18	19
	Immunomodulatory	300	0.9	0.6	67.09	84.23
	Mesenchymal	211	0.71	0.09	14.64	17.45
	Mesenchymal stem-like (MSL)	81	0.86	0.68	18	34.8
	Luminal androgen receptor	253	0.61	0.01	14.7	26.15
	Basal-like (BL1)	251	0.42	9.90E-05	14.85	77.28
CD4	Basal Like (BL2)	101	0.83	0.54	18.18	19
	Immunomodulatory (IM)	300	0.56	0.01	35	114.96
	Mesenchymal (M)	211	0.54	0.0026	12.56	25
	Mesenchymal stem-like (MSL)	81	1.16	0.68	25	24
	Luminal androgen receptor (LAR)	253	0.56	0.0033	16	27
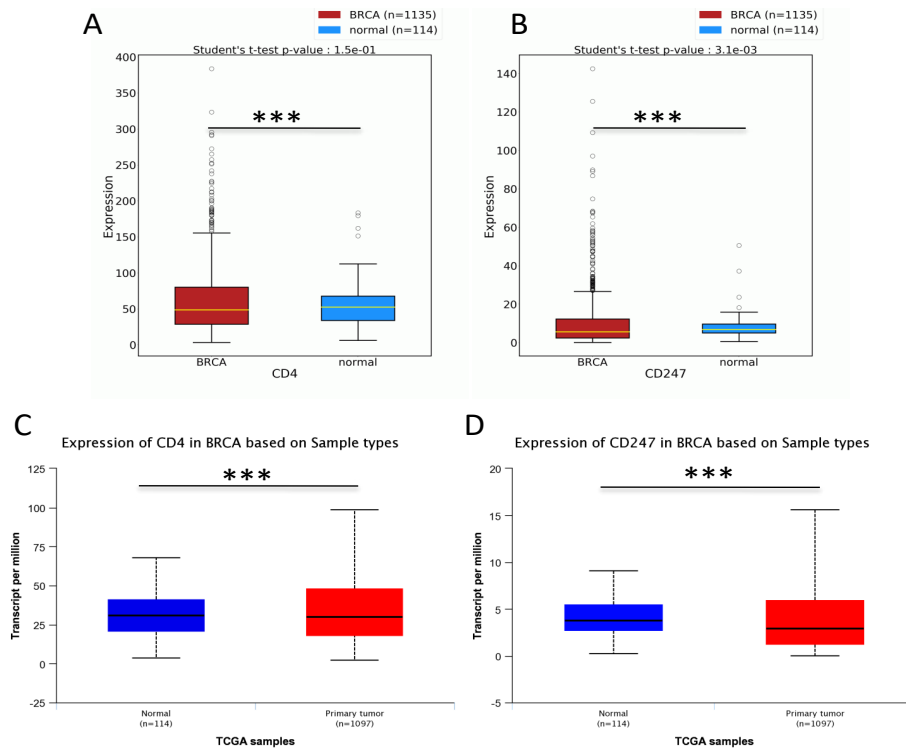
Figure 6. mRNA Expression of *CD4* and *CD247* was Analyzed in Normal Tissue and Primary Tumor from Breast Cancer Patients. (A and B), normal tissue (N=114) and primary breast tumor (N=1135) patients were analyzed by publically available oncoDB database. C and D, normal tissue (N=114) and primary breast tumor (N=1097) patients were analyzed from publicaly available UALCAN database. (P<0.05)

infiltration of the immune cells into tumor stroma in breast cancer has not yet explored. *CD247* is highly expressed in T-cells and NK cells, thus to clarify the TNBC microenvironment and how *CD247* and *CD4* might affect the tumor heterogeneity and prognosis, we investigated the association of *CD247* and *CD4* expression with immune infiltration level in breast cancer. TIMER 2.0 databases was used to estimate the immune infiltration in breast cancer. In basal subtype of BC, expression of *CD247* was positively associated with infiltration B cell (r = 0.691, p = 6.88e-19), CD8+ T cell (r = 0.51, p = 1.67e-09), *CD4*+ T cell (r = 0.25, p = 8.4e-10), neutrophil (r = 0.533, p = 2.00-e09), and dendritic cell (r = 0.63, p = 5.87e-14) (Figure 8A). In addition we evaluated *CD4* expression with immune infiltrating cell markers. The

results indicated that *CD4* expression was correlated with B cell (r = 0.564, p = 9.24e-12), CD8+ T cell (r = 0.509, p = 1.82e-09), *CD4*+ T cell (r = 0.702, p = 2.1e-19), macrophage (r = 0.298, p = 6.80e-04) neutrophil (r = 0.854, p = 2.39e-32), and dendritic cell (r = 0.63, p = 5.87e-14) (Figure 8B). In summary, the above findings suggested that *CD247* and *CD4* expression affect the tumor microenvironment by regulating tumor immune cell infiltration and leads to a poor prognosis.

Discussion

The microenvironment of breast cancer comprises a range of cell types, including TILs. Accumulating evidence indicates that TILs play a critical role in cancer
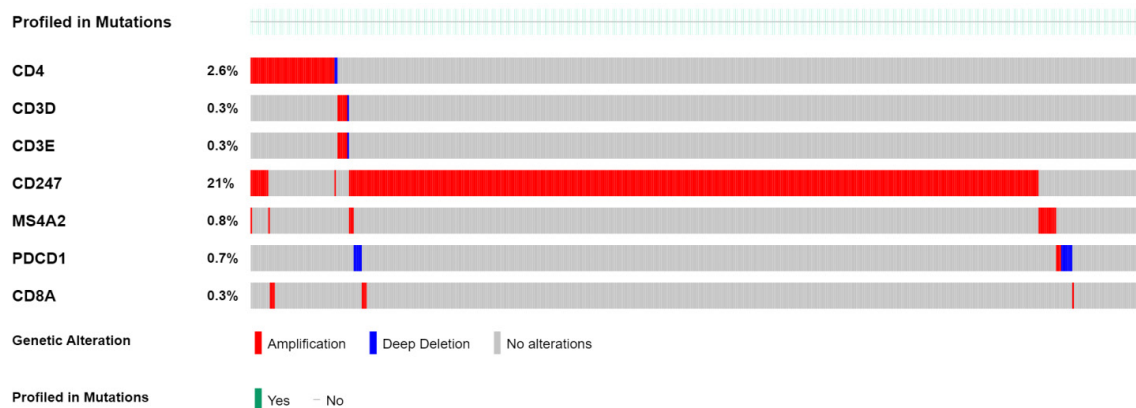

Figure. 7. Genetic Alteration in *CD247* and *CD4* Genes were Analyzed in BC Patients (N= 2051) by c-Bioportal Database. Data is shown in the Oncoprint format.
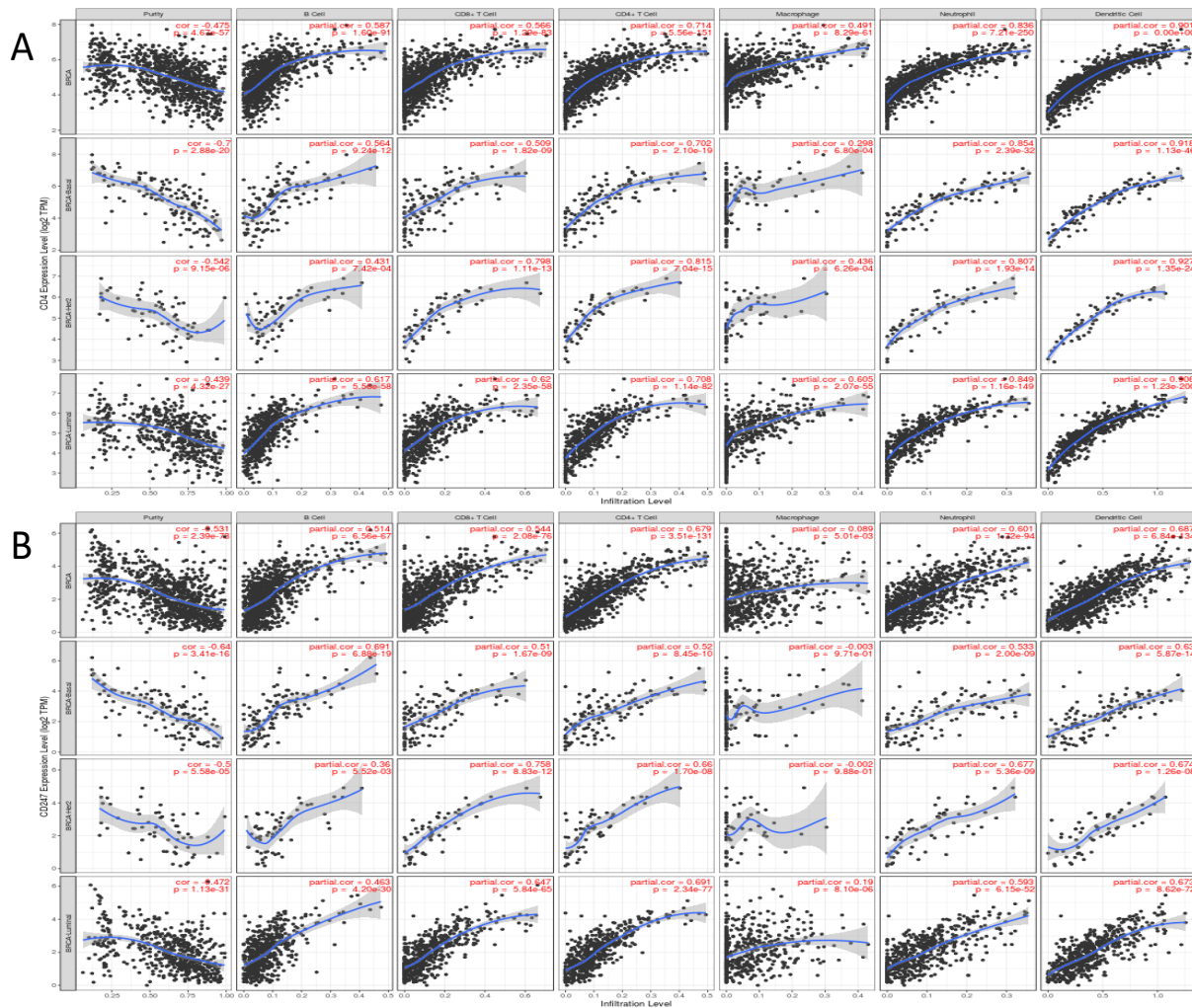
Figure 8. Correlations between *CD4* and *CD247* Expression and Immune Cell Infiltration in Various Breast Cancer Subtypes. (A) Correlations between CD4 (A), CD247 (B) expression and the infiltration of B cells, CD8+T cells, CD4+T cells, macrophages, in BRCA-Luminal A, BRCA-Luminal B, BRCA-basal, BRCA-HER2, breast cancer subtypes.

progression and carcinogenesis [14]. The level of TILs positively associate with the survival outcome of TNBC [31]. Immune cell infiltration in TME varies widely and affects patient's prognosis in terms of OS and RFS. Infiltrating immune cells affects tumors development and metastasis through different signaling pathways [15]. Further, numerous gene alterations have been identified by comparing tumors and normal tissues and cell markers *CD4* and *CD247* showed positive correlation with TILs in TNBC. However, how *CD247*, *CD4* and correlated with TNBC microenvironment and leading to tumor heterogeneity has not thoroughly studied.

TNBCs are clinically aggressive subtypes with high risk of metastasis to visceral organs without particular geographic distribution [32, 33].The presence of TILs within the TME is considered to be an indication of the host immune response to tumors antigens [34]. It was hypothesized that *CD247* could be the basis of T-lymphocyte cell functional deficit. Phosphorylation of *CD247* is an essential step in the intracellular signaling pathway leading to T-lymphocyte activation [35]. The function of *CD247* enhances the TCR signaling cascade and it is necessary for assemble of the TCR/CD3 complex

on the surface of T lymphocytes [36]. It is well-known that an inactive *CD247* leads to impaired T cell activation upon engagement of the TCR [37]. Downregulation of *CD247* has been described in many malignancies such as melanoma, cervical, pancreatic, ovarian, breast, and head and neck cancer. Such abnormal expression of *CD247* is related with differentiation and classification in ovarian cancer [21, 38, 36]

The *CD4* expressed by a subpopulation of monocytes creating a potential bias in the assessment of *CD4* as a specific T-cell marker [39]. The *CD4*-expressing monocytes are primarily investigated in terms of HIV infection and are known to trigger macrophage differentiation, but are also mostly found in peripheral blood and with lower density than seen on T cells. The TCR-CD3 complex on the surface of T lymphocytes is essential for the adaptive immune response. [40]. Upon activation by antigen-presenting cells (APCs), TCR-mediated signals are transmitted across the cell membrane by the CD3 chains (CD3D, CD3E, CD3G and CD3Z). All CD3 chains contain immune receptor tyrosine - based activation motifs in their cytoplasm domain. Upon TCR engagement, these motifs become phosphorylated by Src

family protein tyrosine kinases LCK and FYN, resulting in the activation of downstream signaling pathways [35, 41]. CD3Z ITAMs phosphorylation creates multiple docking sites for the protein kinase ZAP70 leading to ZAP70 phosphorylation and its conversion into a catalytically active enzyme. Thus, in initial stage decreased expression of CD3 zeta and impairment of T-cell function were detected in tumour-infiltrating lymphocytes [20].

CD247, also known as T-cell antigen receptor zeta (TCR-Z) or CD3 zeta-chain (CD3), is an integral element of T-cell Receptor (TCR) complex that is crucial component in the structure, expression and function of TCR and NK cell-activating receptor [35]. *CD247* recruits tyrosine kinases, which in turn triggers a number of downstream signaling cascades that potentially activate T-cells [42]. *CD247* is essential for the activation of antigenic peptide presented by the human leukocyte antigen on APCs or tumor cells. Downregulation of *CD247* is often found to be followed by reduced expression of other T-cell-associated signal-transuding molecules, like ZAP-70 and p56lck, decreased calcium flux and T-cell apoptosis [16]. The ability of cancer cells to evade the action of the immune system is one of the most challenging aspects of cancer and its treatment. Decreased *CD247* expression is linked to several types of cancer, such as renal carcinoma, gastric carcinoma, melanoma, breast cancer, pancreatic cancer, cervical cancer, ovarian cancer, head and neck cancer, B-cell lymphoma, and B-cell lymphoma [21, 36].

The presence of TILs is associated with a better prognosis in cancer patients as it is an indication that the patient's immune system is functioning and is reacting to the cancer antigens. A recent study showed that the expression of *CD247* in peripheral blood lymphocytes from patients with ovarian cancer is decreased compared with ovarian cyst patients and the expression of *CD247* in tumor infiltrating lymphocytes with cancer tissue is decreased compared with adjacent tissues. This showed that abnormal expression of *CD247* was related with differentiation and classification in ovarian cancer [35]. In breast cancer, data is not available on the correlation between *CD247* expression and breast cancer stages. According to the Kaplan-Meier survival analysis the low mRNA expression of *CD247* is associated with worse prognosis in breast cancer. The amplification and transcriptional upregulation of *CD247* has a high correlation with their mRNA expression. Survival analysis indicated that high mRNA expression of *CD247* was associated with good prognosis in patients with breast cancer, specifically in basal subtype of breast cancer. Thus, *CD247* amplification predicts good survival outcome in BC.

CD247 and *CD4* are the critical components of T- cell receptors. Our findings for the first time link the prognostic significance of these surface immune markers to the poor prognosis of TNBC. The low levels of *CD247* and *CD4* provide a significant indication of decreased infiltration of immune cells into the TME. This observation has implications on cancer cell clearance and subsequent immune evasion of these cells leading to increased metastasis. This result in much shorter relapse- free survival and overall survival of TNBC patients compared to the patients with higher expression of these genes. *CD247* and *CD4* may be relevant as a biomarker for the progression of TNBC and can be potentially targeted as a potential treatment strategy for TNBC.

Author Contribution Statement

AS and AK: Conception, study design, interpretation of data, and critical evaluation of the manuscript. AP and RN: Analysis and interpretation of data.AS, AK, AP and RN: Preparation of the Manuscript. All authors concur with the final version of the manuscript.

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Conflict of Interest
The authors declare no conflict of interest.

Ethical clearance
Not required as no biological samples or specimen was used in this study.

Abbreviations
BC: Breast cancer
EGA: European genome-phenome archive
GEO: Gene Expression Omnibus
OS: Overall survival
RFS: Relapse-free survival
TCGA: The cancer genome atlas
TNBC: Triple-negative breast cancer
TCR: T-cell receptor
TILs: Tumor-infiltrating lymphocytes
ZAP 70: Zeta-chain associated protein kinase 70kDa

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