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Identification of Predictive Factors for Late Radiotherapy-Induced Complications in Post-Mastectomy Breast Cancer Survivors

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A B S T R A C T

Introduction: Post-mastectomy radiotherapy significantly improves locoregional control and survival in breast cancer patients but may lead to late complications such as fibrosis, cardiopulmonary toxicity, and lymphedema, which adversely affect long-term quality of life. Identifying patients at higher risk is essential for personalized survivorship care. This study aims to determine predictive factors for late radiotherapy-induced complications in post-mastectomy breast cancer survivors.

Material and methods: This cross-sectional analytical study was conducted in 2025 at hospitals affiliated with Tabriz University of Medical Sciences and included 73 post-mastectomy breast cancer survivors. The study evaluated predictive factors for late radiotherapy-induced complications using demographic, clinical, surgical, oncologic, and dosimetric variables, along with treatment-related characteristics and late toxicity outcomes.

Results: Among 73 post-mastectomy survivors, late complications were common, particularly skin fibrosis (30.14%) and shoulder limitation (28.77%). Severe toxicity (CTCAE ≥2) occurred in 35.62% and was associated with higher BMI (P=0.004), smoking (P=0.037), mean heart dose (P=0.001), and lung V20 (P=0.002). Lung V20 predicted severe events (AUC=0.84; cut-off=20.57%; sensitivity=84.62%; specificity=72.34%).

Conclusion: Late radiotherapy-induced complications remain prevalent in post-mastectomy breast cancer survivors. Elevated BMI, smoking, and higher cardiopulmonary dose parameters particularly lung V20 were associated with severe toxicity. These findings highlight the importance of optimizing radiation planning and addressing modifiable risk factors to reduce long-term morbidity and improve survivorship outcomes.

Introduction

Breast cancer has evolved from a rapidly fatal disease into a condition with high long-term survival, owing to advancements in early detection, systemic therapies, and increasingly precise radiotherapy. As treatment outcomes have improved, the attention of modern oncology has shifted toward optimizing long-term quality of life and preventing late treatment-related morbidity in survivors. Post-mastectomy radiotherapy (PMRT) plays a central role in reducing loco regional recurrence and improving overall survival, yet its benefits are accompanied by the risk of late-onset, often irreversible complications that may emerge months or years after treatment completion (1,2).

The therapeutic objective of PMRT is to eradicate microscopic residual disease within the chest wall and regional lymphatics; however, the close proximity of critical structures creates an inherent challenge in sparing healthy tissues from radiation exposure. Late toxicities are distinguished from acute effects by their progressive, chronic nature,

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shaped by persistent inflammation, microvascular injury, and aberrant fibrosis. Unlike transient erythema or desquamation observed during treatment, late effects often impair function, disrupt daily life, and may continue to worsen over decades, underscoring the need to identify individuals at increased risk before damage becomes irreversible (3,4).

Cutaneous and subcutaneous changes remain the most prevalent late complications following PMRT in post-mastectomy survivors. These range from telangiectasia and persistent pigmentation abnormalities to severe radiation-induced fibrosis (RIF), a debilitating condition characterized by tissue induration, restricted shoulder mobility, neuropathic pain, and functional deficits. The pathogenesis of RIF driven by dysregulated cytokine signaling particularly the overexpression of transforming growth factor-beta (TGF-β) which promotes fibroblast activation and excessive extracellular matrix deposition. Early recognition of patients predisposed to fibrotic changes is critical for tailoring preventive strategies and rehabilitation programs (5,6).

Beyond superficial tissue damage, PMRT may also lead to deep organ toxicities, primarily involving the cardiovascular and pulmonary systems. Left-sided breast cancer survivors are particularly vulnerable to radiation-induced heart disease (RIHD), including coronary artery stenosis, valvular injury, and pericardial thickening. Similarly, irradiation of thoracic structures increases the risk of pneumonitis and late pulmonary fibrosis, which manifest as chronic dyspnea and reduced exercise tolerance. Despite the introduction of advanced delivery techniques, such as Deep Inspiration Breath Hold (DIBH) and intensity-modulated radiotherapy, a residual risk remains due to cumulative exposure of these organs to low and moderate radiation doses (7,8).

Lymphedema represents another major late complication that significantly affects survivors' quality of life. PMRT, especially when combined with axillary lymph node dissection, can disrupt lymphatic drainage pathways and result in chronic swelling of the ipsilateral arm. The condition is associated with pain, reduced mobility, heightened infection risk, and long-term psychological distress. Because lymphedema often develops gradually, identifying early predictors such as high BMI, extensive nodal involvement, or increased lymphatic radiation doses is necessary for initiating timely interventions and preventing functional decline (9,10).

A growing body of research highlights the importance of patient-related factors in shaping susceptibility to late radiotherapy complications. Age, obesity, smoking history, and pre-existing comorbidities have each linked to altered tissue radio sensitivity. For example, obesity creates a chronic pro-inflammatory state that may exacerbate radiation injury, while diabetes mellitus impairs microvascular repair and increases the risk of delayed healing. Autoimmune and connective tissue disorders further amplify susceptibility due to underlying collagen abnormalities and chronic systemic inflammation, emphasizing the complex interaction between biological vulnerability and radiation exposure (11, 12).

Treatment-related variables also play a decisive role in determining long-term toxicity. The transition from two-dimensional radiotherapy to Three-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity-Modulated Radiotherapy (IMRT) has refined dose delivery but cannot entirely eliminate the "low-dose bath" to surrounding tissues. Additional factors including total chest wall dose, the use of tissue-equivalent bolus to enhance surface dosing, and the sequencing of radiotherapy with systemic therapies such as anthracyclines, taxanes, or HER2-directed biologics may synergistically increase toxicity risk. These interactions highlight the importance of considering the cumulative treatment burden rather than radiotherapy alone (13,14).

Emerging evidence suggests that genetic predisposition influences the development of late radiotherapy complications, prompting investigations into radio sensitivity biomarkers. Genetic polymorphisms in DNA repair genes (e.g., ATM), oxidative stress regulators (e.g., SOD2), and cytokine pathways (e.g., TGFB1) have been associated with increased rates of fibrosis, telangiectasia, and tissue breakdown. Understanding the genomic determinants of radiation response could enable a shift toward radio genomics-based risk stratification, allowing personalized radiotherapy planning and proactive management of high-risk individuals (15,16).

Late radiotherapy complications also impose substantial psychological, social, and economic burdens on survivors. Chronic pain, cosmetic disfigurement, and functional limitations can lead to emotional distress, reduced self-confidence, and diminished social participation. Many survivors face increased medical expenses, physical therapy needs, and reduced workplace productivity. Because these long-term consequences are often underreported, identifying predictors of late toxicity is essential not only for physical health but also for improving holistic survivorship outcomes (17,18).

From a dosimetric perspective, predictive modeling has become an essential tool for estimating late complication risk. Parameters such as mean heart dose (MHD), lung V20, and chest wall surface dose frequently used in clinical decision-making. However, these metrics may fail to capture micro-regional dose variations or the complex spatial distribution of radiation exposure. Recently, radiomics-based approaches and machine-learning

tools have emerged as promising methods for extracting detailed structural and textural features from planning CT scans, enabling more accurate prediction of organ-specific late effects (19, 20).

Despite extensive research on acute toxicities, late complications remain under-investigated, particularly in the context of contemporary surgical and reconstructive practices. The increasing use of immediate breast reconstruction, including implant-based or autologous techniques, adds new complexity to radiotherapy planning. Radiation can contribute to capsular contracture, flap fibrosis, or reconstructive failure, complicating both aesthetic and functional outcomes. As reconstructive trends evolve, updated predictive models that incorporate surgical variables are critically needed to support modern multidisciplinary decision-making (21,22).

Another challenge in understanding late toxicities is the limited duration of follow-up in many clinical trials. Since complications such as cardiac disease or fibrosis may emerge decades after treatment, short-term studies fail to capture the full trajectory of late effects. Longitudinal survivorship cohorts and dedicated follow-up programs are essential to bridging this "latency gap." Large datasets may also support more accurate identification of early clinical and dosimetric markers that precede visible deterioration, enabling preemptive intervention before severe damage occurs (23,24).

Within the precision medicine era, optimizing the therapeutic ratio in breast cancer care hinges on balancing effective tumor control with minimization of late harm. Predicting which survivors are most likely to develop chronic complications is a prerequisite for individualized radiotherapy planning, targeted surveillance, and timely rehabilitation. Integrating clinical risk factors with dosimetric metrics and emerging genomic data represents a transformative strategy for tailoring treatment intensity and protecting long-term quality of life. This patient-centered approach is increasingly recognized as essential in modern oncology (25,26).

The present study designed to address these unmet needs by identifying key predictors of late radiotherapy-induced complications in post-mastectomy breast cancer survivors. Through comprehensive evaluation of patient demographics, treatment characteristics, and dosimetric parameters, it aims to clarify which factors most strongly influence long-term toxicity risk. By employing a multifactorial analytical approach, the study seeks to provide clinicians with a practical predictive framework to support individualized follow-up strategies and to enhance the long-term well-being of the growing population of breast cancer survivors.

Material and methods

Study Design

This research conducted as a cross-sectional analytical study in hospitals affiliated with Tabriz University of Medical Sciences during 2025. The study focused on post-mastectomy breast cancer survivors who had previously received post-mastectomy radiotherapy, aiming to identify predictive factors for late radiotherapy-induced complications.

Sampling

Convenience sampling was used to recruit eligible participants from oncology, radiotherapy, and surgical follow-up clinics. The sample size was determined using the standard formula for estimating prevalence in a single population (the sample-size formula for prevalence estimation), based on assumptions including a presumed prevalence, a 95% confidence level, and a specified margin of error. Under these assumptions, a final sample size of 73 participants obtained.

Eligibility Criteria

Inclusion criteria: adult women aged 18 years or older; history of unilateral modified radical mastectomy or simple mastectomy; receipt of adjuvant post-mastectomy radiotherapy completed at least one-year prior; availability of complete radiotherapy and clinical records; and willingness to participate with signed informed consent. Exclusion criteria included: recurrent or metastatic breast cancer; prior thoracic radiotherapy for any reason; significant pre-existing cardiopulmonary disease unrelated to radiotherapy; known connective tissue disorders (such as scleroderma or lupus); active infection or lymphedema unrelated to cancer treatment; prior breast-conserving surgery; immediate reconstructive procedures using autologous flaps or implants that complicate complication attribution; and inability to undergo clinical evaluation.

Procedures

All participants underwent standardized clinical assessment and structured interviews to collect demographic variables (age, BMI, smoking history, comorbidities), cancer-related variables (tumor stage, nodal status, histopathology), treatment variables (type of mastectomy, chemotherapy regimens, hormone therapy, HER2-directed therapy), and detailed radiotherapy parameters (total dose, fractionation, boost dose, radiation technique, mean heart dose, ipsilateral lung V20, chest wall surface dose). Mastectomy procedures in this cohort primarily followed standard oncologic principles: removal of the entire breast tissue with or without axillary lymph node dissection, depending on tumor burden and surgeon judgment. Late complications assessed included cutaneous fibrosis, telangiectasia,

chest wall induration, lymphedema, pulmonary symptoms, and cardiac-related manifestations. Clinical evaluations supplemented by imaging and laboratory data when indicated.

Statistical Analysis

Data analysis performed using appropriate statistical tests based on variable type and distribution. Normality assessed using the Shapiro–Wilk test. Descriptive statistics (means, standard deviations, medians, frequencies) generated for all variables. Between-group comparisons were analyzed using t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Logistic regression analysis performed to identify independent predictors of late radiotherapy complications. Multivariable models included variables with P<0.20 in univariate analyses. Receiver Operating Characteristic (ROC) curves used to assess predictive performance of significant dosimetric parameters. A P-value <0.05 was considered statistically significant.

Ethical Considerations

The study approved by the Ethics Committee of Tabriz University of Medical Sciences, and all participants provided informed written consent. Ethical approval code: IR.TBZMED.FMD.REC.1404.058.

Results

The baseline characteristics of the study cohort (n = 73) revealed a mean age of 54.82 ± 9.47 years and a mean BMI of 28.16 ± 4.38 kg/m². Most participants were married (69.86%), never smokers (79.45%), and had Stage II (42.47%) or Stage III (36.99%) disease. Comorbidities such as hypertension and diabetes were present in 28.77% and 19.18% of the patients, respectively, while the majority exhibited hormone receptor-positive tumors (ER+ 67.12%; PR+ 58.90%) (table 1).

Table 1. Baseline Demographic, Clinical and Tumor Characteristics of Post-Mastectomy Breast Cancer Survivors

Variable	Category / Value	n (%) or Mean ± SD
Age (years)	-	54.82 ± 9.47
BMI (kg/m²)	-	28.16 ± 4.38
Marital status	Married	51 (69.86)
-	Single	8 (10.96)
-	Widowed	10 (13.70)
-	Divorced	4 (5.48)
Educational level	Primary school or less	24 (32.88)
-	Secondary school	19 (26.03)
-	High school diploma	17 (23.29)
-	University education	13 (17.81)
Smoking status	Never smoker	58 (79.45)
-	Former smoker	9 (12.33)
-	Current smoker	6 (8.22)
Diabetes mellitus	Yes	14 (19.18)
-	No	59 (80.82)
Hypertension	Yes	21 (28.77)
-	No	52 (71.23)
Tumor stage	Stage I	9 (12.33)
-	Stage II	31 (42.47)
-	Stage III	27 (36.99)
-	Stage IV*	6 (8.22)
Histologic grade	Grade I	11 (15.07)
-	Grade II	38 (52.05)
-	Grade III	24 (32.88)
ER status	Positive	49 (67.12)
-	Negative	24 (32.88)
PR status	Positive	43 (58.90)
-	Negative	30 (41.10)
HER2 status	Positive	21 (28.77)
-	Negative	52 (71.23)

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SD, standard deviation.

The treatment profile of the cohort showed that most patients underwent modified radical mastectomy (65.75%), followed by simple mastectomy (23.29%). The most common chemotherapy regimen was anthracycline plus taxane (42.47%), while 38.36% received tamoxifen as hormone therapy. Radiotherapy mainly delivered using 3D-CRT (60.27%). The mean total radiation dose was 49.86 ± 3.41 Gy across 24.73 ± 2.18 fractions, with a mean heart dose of 4.18 ± 1.27 Gy and an ipsilateral lung V20 of 21.64 ± 6.52% (table 2).

Table 2. Treatment Characteristics and Radiotherapy Parameters among Post-Mastectomy Breast Cancer Survivors

Variable	Category / Value	n (%) or Mean ± SD
Type of mastectomy	Modified radical mastectomy	48 (65.75)
-	Simple mastectomy	17 (23.29)
-	Skin-sparing mastectomy	8 (10.96)
Chemotherapy regimen	Anthracycline-based	29 (39.73)
-	Anthracycline + taxane	31 (42.47)
-	Taxane-based only	8 (10.96)
-	No chemotherapy	5 (6.85)
Hormone therapy	Tamoxifen	28 (38.36)
-	Aromatase inhibitor	21 (28.77)
-	Sequential therapy	9 (12.33)
-	None	15 (20.55)
Radiotherapy technique	3D-CRT	44 (60.27)
-	IMRT	29 (39.73)
Total radiation dose (Gy)	-	49.86 ± 3.41
Number of fractions	-	24.73 ± 2.18
Mean Heart Dose (Gy)	-	4.18 ± 1.27
Ipsilateral Lung V20 (%)	-	21.64 ± 6.52

Abbreviations: 3D-CRT, three-Dimensional Conformal Radiotherapy; IMRT, Intensity-Modulated Radiotherapy; Gy, Gray; V20, percentage of lung volume receiving ≥20 Gy; SD, standard deviation.

In this cohort of 73 post-mastectomy breast cancer survivors, late radiotherapy-related complications were frequent, with skin fibrosis affecting 30.14% of participants and lymphedema occurring in 19.18%. Telangiectasia and shoulder mobility limitation also observed in clinically meaningful proportions, while cardiopulmonary toxicity remained relatively uncommon but still present, underscoring the long-term burden of radiation exposure (table 3).

Table 3. Prevalence and Severity of Late Radiotherapy-Induced Complications among Post-Mastectomy Breast Cancer Survivors

Complication	CTCAE Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total Affected n (%)
Skin fibrosis	51 (69.86)	12 (16.44)	8 (10.96)	2 (2.74)	22 (30.14)
Telangiectasia	58 (79.45)	10 (13.70)	4 (5.48)	1 (1.37)	15 (20.55)
Lymphedema	59 (80.82)	9 (12.33)	4 (5.48)	1 (1.37)	14 (19.18)
Shoulder motion limitation	52 (71.23)	13 (17.81)	6 (8.22)	2 (2.74)	21 (28.77)
Cardiopulmonary toxicity	63 (86.30)	6 (8.22)	3 (4.11)	1 (1.37)	10 (13.70)

In the univariate analysis of the 73 post-mastectomy breast cancer survivors, 26 patients (35.62%) developed severe late complications (CTCAE ≥ Grade 2), while 47 patients (64.38%) had no or only mild complications. Several demographic, clinical, and treatment-related variables showed statistically significant associations with severe toxicity, particularly body mass index, smoking status, radiotherapy technique, mean heart dose, and ipsilateral lung V20, suggesting potential predictors for further multivariable evaluation (table 4).

Table 4. Univariate Analysis of Factors Associated with Severe Late Radiotherapy-Induced Complications

Variable	No/Mild Complication (n = 47)	Severe Complication (n = 26)	P value
Age (years), Mean ± SD	53.41 ± 8.96	57.28 ± 10.11	0.083
BMI (kg/m²), Mean ± SD	26.97 ± 3.82	30.11 ± 4.27	0.004
Current smoker, n (%)	4 (8.51)	7 (26.92)	0.037
Diabetes mellitus, n (%)	7 (14.89)	7 (26.92)	0.214
Hypertension, n (%)	11 (23.40)	10 (38.46)	0.166
Stage III disease, n (%)	17 (36.17)	13 (50.00)	0.241
Modified radical mastectomy, n (%)	29 (61.70)	19 (73.08)	0.323
Anthracycline + taxane chemotherapy, n (%)	19 (40.43)	12 (46.15)	0.635
Hormone therapy use, n (%)	35 (74.47)	18 (69.23)	0.628
IMRT technique, n (%)	16 (34.04)	13 (50.00)	0.176
Total radiation dose (Gy), Mean ± SD	49.12 ± 3.18	50.63 ± 3.67	0.072
Mean heart dose (Gy), Mean ± SD	3.71 ± 1.05	5.02 ± 1.36	0.001
Ipsilateral lung V20 (%), Mean ± SD	19.47 ± 5.21	24.89 ± 6.38	0.002

Abbreviations: BMI, body mass index; IMRT, intensity-modulated radiotherapy; Gy, Gray; V20, percentage of lung volume receiving ≥20 Gy; SD, standard deviation.

In this analysis, ipsilateral lung V20 showed good discriminative ability for predicting severe late radiotherapy-induced complications, with an AUC of 0.84. The optimal cut-off point was 20.57%, yielding a sensitivity of 84.62% and a specificity of 72.34%, suggesting that higher lung dose exposure is meaningfully associated with the risk of severe toxicity (figure 1).

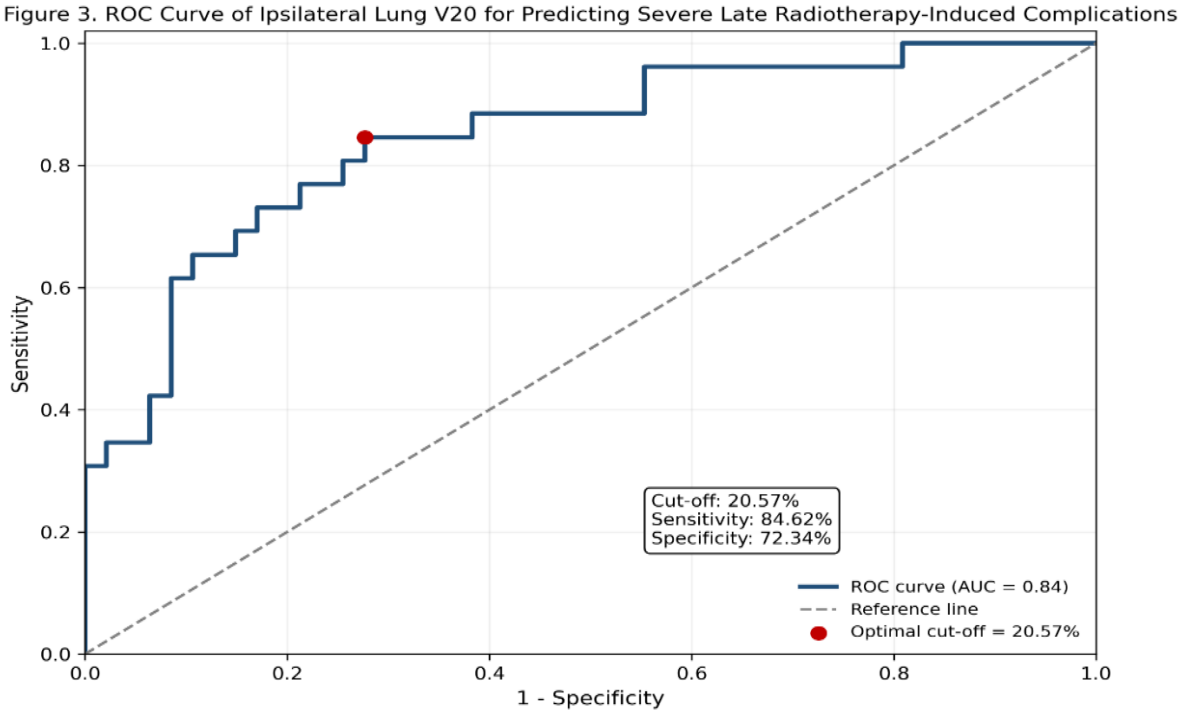

Figure 1. Receiver Operating Characteristic (ROC) Curve for Ipsilateral Lung V20 as a Predictor of Severe Late Radiotherapy-Induced Complications

The distribution of Body Mass Index (BMI) differed significantly based on the severity of late skin fibrosis, with a noticeably higher median BMI observed in the severe fibrosis group. Specifically, patients with severe fibrosis (CTCAE ≥ Grade 2) had a significantly higher BMI compared to those with no or mild fibrosis (P<0.01), suggesting that higher adiposity may exacerbate the chronic inflammatory response following radiotherapy (figure 2).

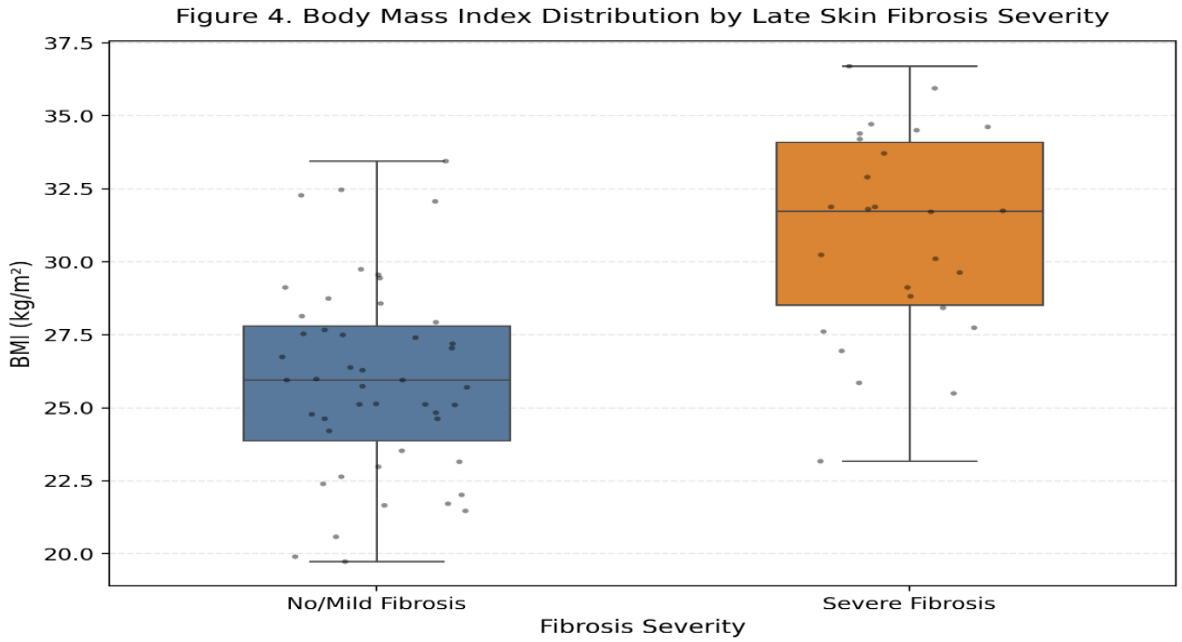

Figure 2. Distribution of Body Mass Index (BMI) Stratified by Severity of Late Skin Fibrosis

Discussion

The present study demonstrated that late radiotherapy-related complications remain a substantial clinical issue among post-mastectomy breast cancer survivors. Cutaneous fibrosis and shoulder dysfunction among the most frequently observed sequelae, while lymphedema and telangiectasia also occurred in a notable proportion of patients. Cardiopulmonary toxicity was less common but still clinically relevant. Severe complications were associated with higher body mass index, smoking, and increased cardiopulmonary radiation exposure, particularly elevated mean heart dose and ipsilateral lung V20. Moreover, lung V20 showed good discriminatory performance for predicting severe toxicity, and patients with severe fibrosis exhibited a distinctly higher BMI distribution.

These findings are biologically plausible and consistent with the pathophysiological mechanisms underlying radiation-induced late tissue injury. Radiotherapy produces persistent microvascular damage, fibroblast activation, and extracellular matrix remodeling, leading to progressive fibrosis and tissue stiffness months to years after exposure. Chronic upregulation of profibrotic cytokines such as transforming growth factor-β promotes collagen deposition and my fibroblast differentiation, ultimately manifesting as induration, skin retraction, and impaired mobility. The relatively high prevalence of skin fibrosis and shoulder limitation in our cohort likely reflects this sustained fibro genic cascade, particularly in patients exposed to higher regional doses or with host susceptibility factors that amplify inflammatory signaling (27).

The association between elevated BMI and severe late toxicity deserves particular attention. Adipose tissue is not metabolically inert; it functions as an active endocrine organ that secretes pro-inflammatory mediators including interleukin-6 and tumor necrosis factor-α, thereby maintaining a state of low-grade systemic inflammation. In the context of radiotherapy, this pro-inflammatory milieu may intensify oxidative stress and endothelial dysfunction, enhancing fibroblast activation and impairing tissue repair. Increased subcutaneous thickness may also alter dose distribution and oxygenation patterns, potentially creating microenvironments more vulnerable to chronic radiation injury. The higher BMI observed in patients with severe fibrosis in our study therefore likely reflects both biological and dosimetric interactions that converge on exaggerated fibrotic remodeling (28).

Smoking emerged as another clinically meaningful correlate of severe complications. Tobacco exposure is known to impair microvascular perfusion, reduce tissue oxygenation, and disrupt collagen homeostasis. Nicotine-induced vasoconstriction and carbon monoxide-related hypoxia can compromise post-radiation healing capacity, thereby amplifying chronic inflammation and fibrosis. Furthermore, smoking has been associated with increased pulmonary susceptibility to radiation injury, potentially explaining its relationship with more severe toxicity in patients receiving chest wall irradiation. The detrimental vascular and immunomodulatory effects of smoking provide a coherent explanation for its contribution to late adverse outcomes in this population (29).

Dosimetric parameters, particularly mean heart dose and ipsilateral lung V20, demonstrated strong associations with severe toxicity. These findings underscore the central role of radiation exposure volume in shaping late organ damage. Lung V20 reflects the proportion of pulmonary tissue receiving at least 20 Gy and is widely recognized as a predictor of radiation pneumonitis and long-term pulmonary dysfunction. Higher V20 values imply broader parenchymal exposure, leading to diffuse inflammatory infiltration, alveolar damage, and eventual fibrotic transformation. The robust discriminative performance of V20 in our ROC analysis suggests that even within contemporary treatment ranges, incremental increases in lung exposure materially influence long-term complication risk (30).

Similarly, elevated mean heart dose may contribute to subclinical myocardial fibrosis, microvascular rarefaction, and endothelial injury, processes that can manifest clinically as cardiopulmonary toxicity over time. Although overt cardiac events were not highly prevalent in our cohort, the observed association between higher cardiac dose and severe overall toxicity likely reflects the interconnected nature of thoracic radiation injury. Cardiac and pulmonary tissues share overlapping vascular and inflammatory pathways, and dose spillover into adjacent structures may amplify cumulative organ stress. These observations reinforce the importance of meticulous treatment planning aimed at minimizing heart and lung exposure without compromising oncologic control (31).

The relatively lower frequency of severe cardiopulmonary complications compared with cutaneous and musculoskeletal sequelae may be attributable to advances in radiotherapy techniques. The use of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy allows improved dose homogeneity and sparing of organs at risk. Nevertheless, our data indicate that technique alone does not eliminate risk; rather, the achieved dosimetric parameters determine clinical outcome. This distinction highlights the need for individualized optimization and adherence to evidence-based dose constraints, particularly in patients with additional risk modifiers such as obesity or smoking history (32).

Shoulder mobility limitation observed in our study likely reflects a multifactorial process involving fibrosis of the chest wall, axillary tissues, and per articular structures. Surgical disruption of lymphatic drainage combined with radiation-induced soft tissue stiffening can restrict glen humeral excursion. Over time, reduced mobility may further perpetuate fibrosis through decreased mechanical stretching and altered tissue remodeling. Early physiotherapy and rehabilitation interventions may therefore play a crucial preventive role, especially in patients identified as high risk based on clinical or dosimetric profiles (33).

From a clinical perspective, the identification of a V20 cut-off with favorable sensitivity and specificity provides a practical threshold for risk stratification. While no single parameter fully predicts late toxicity, integrating lung V20, mean heart dose, BMI, and smoking status into predictive models could enhance individualized counseling and surveillance strategies. Patients exceeding established cut-offs may benefit from intensified follow-up, early symptom evaluation, and targeted lifestyle interventions aimed at modifiable factors such as weight control and smoking cessation. Such preventive approaches align with the broader survivorship paradigm that prioritizes long-term quality of life alongside oncologic outcomes (34).

Several limitations acknowledged when interpreting these findings. The cross-sectional design limits causal inference, and late complications may evolve over extended follow-up periods beyond the study window. The sample size, although adequate for exploratory analysis, may restrict the precision of subgroup estimates. Additionally, unmeasured biological factors such as genetic radio sensitivity or baseline inflammatory biomarkers not assessed. Despite these constraints, the coherent pattern of clinical and dosimetric associations observed in our study strengthens the validity of the conclusions and provides a foundation for prospective, multicenter investigations (35).

In summary, our findings indicate that late radiotherapy-induced complications remain prevalent among post-mastectomy breast cancer survivors and are influenced by a combination of host characteristics and radiation exposure parameters. Elevated BMI, smoking, and increased cardiopulmonary dose metrics appear to amplify the risk of severe toxicity through mechanisms involving chronic inflammation, microvascular injury, and progressive fibrosis. Optimizing dose distribution and addressing modifiable risk factors may therefore reduce long-term morbidity and improve survivorship outcomes in this growing patient population (36).

Conclusion

This study demonstrates that late radiotherapy-related morbidity continues to affect a substantial proportion of post-mastectomy breast cancer survivors. Severe complications were strongly associated with modifiable host factors such as obesity and smoking, as well as treatment-related dosimetric parameters, especially mean heart dose and ipsilateral lung V20. The predictive performance of lung V20 suggests that careful adherence to dose constraints may meaningfully reduce long-term toxicity. Integrating individualized radiation planning with lifestyle modification strategies may enhance quality of life

and minimize chronic adverse effects in breast cancer survivorship care.

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Conflicts of interest
The authors declare that they have no competing interests.

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Authors' Contributions
All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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