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REVIEW ARTICLE

Bladder Cancer Molecular Classification: Current Status and Future Prospects

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ABSTRACT

Background: To advance the use of recent discoveries in clinical setting, it is crucial to establish a consensus regarding the molecular classification of bladder cancer (BC). BC remains a significant global public health issue. It ranks as the 10th most frequently diagnosed cancer and the 13th leading cause of cancer-related deaths globally. Efforts are underway to develop classification systems for non-muscle invasion bladder cancer (NMIBC) and muscle invasion bladder cancer (MIBC) due to the significant differences in treatment approaches. **Conclusions**: We conducted a search through various scientific websites, including original papers and clinical trials, to explore the classification journey of bladder cancer and the rationale for each subtype. Most of the molecular classifications are highlighted in the following manuscript aiming to be of significant value in near future in treatment strategies to improve the outcome. Further clinical trials focusing on the impact of molecular classification are urgently needed to advance the understanding and treatment of BC.
Keywords: Bladder cancer; Molecular classification; NMIBC, MIBC

INTRODUCTION

Bladder Cancer (BC) is one of the most common cancers, particularly in men with the median age at diagnosis is 73 years, often accompanied by various comorbidities. It ranks as the 10th most frequently diagnosed cancer and the 13th leading cause of cancer-related deaths globally [1].

BC is also associated with high economic costs due to the extensive therapy and following up it necessitates. This places a significant burden on both patients and healthcare systems [2]. It is a diverse disease, with over 90% of cases being urothelial carcinoma (UC) and the rest being neuroendocrine tumours, adenocarcinoma, or squamous cell carcinoma [3].

Various genetic and molecular subtypes of BC have been identified through extensive profiling initiatives, including The Cancer Genome Atlas project. However, due to a lack of data substantiating their added predictive and prognostic value; these subtypes are not yet frequently taken into account in clinical practice [4].

Predicting which patients will not respond to therapy upfront is a crucial unmet need, particularly with the growing number of elderly patients with co-morbidities facing an increased risk of refractory cancers, which may be related to molecular basis [5].

In the past 5 years, significant developments have occurred in our understanding of BC. Previously, our knowledge was limited to histopathology, with pathologists categorizing BC as NMIBC or MIBC based on morphology of the cell and degree of invasion [6].

In this review, we discuss the latest developments in understanding BC, with a focus on NMIBC and MIBC types. The field is evolving quickly, offering hope for significant progress in treating this disease.

Historical Context and Current Trends:

BC is traditionally divided into two categories: NMIBC, which are restricted to the submucosal connective tissue or mucosa, and MIBC (Figure 1), which invade through the muscle layer. MIBC represents about 25% of newly diagnosed cases, while NMIBC makes up the remaining 75%. Patients with NMIBC generally have a favorable prognosis. For patients with grade 1, grade 2, and grade 3 tumors, the 5-year specific mortality rates are 0.5%, 1.7%, and 6.8%, respectively [7].

NMIBC is mainly treated with intravesical therapies and repeat transurethral resections (TURBT) to

prevent progression to MIBC. Patients with MIBC either de-novo or evolutes may undergo neoadjuvant chemotherapy (NAC) by platinum-based followed by radical cystectomy (RC), or in some cases, tri-modal therapy involving chemotherapy (CTH), radiotherapy (RT), and TURBT [8].

Despite local therapy, NMIBC may progress to MIBC, leading to lower survival rates compared to de novo cases (5-year overall survival (OS) 37% versus 49%). This progression occurs in up to 40% of high-risk NMIBC cases. MIBC patients have a dismal prognosis (5-year OS <50%) with limited advancements in treatment outcomes over recent years [9].

Platinum-based CTH is the standard treatment for advanced or metastatic MIBC. Immune checkpoint inhibitors (ICIs) are also used. Although, there have been advancements in BC management and ICIs have shown survival benefit, the overall impact on survival outcomes is modest.

After basic histopathologic assessment, cytogenetic evaluations delved into molecular alterations in different stages of BC. Gene alteration studies using the polymerase chain reaction (PCR), sequencing techniques and comparative genomic hybridization (CGH) furthered our understanding. Cytogenetic studies distinguished MIBC and NMIBC, revealing unique mutational pathways for each.

Genetic susceptibility:

BC is generally not considered to have a significant genetic basis. However, there are rare cases of monogenic susceptibility. Studies have shown that individuals with the retinoblastoma gene (RB) mutations or those with bilateral retinoblastoma have a notably higher risk of its development. However, a recent long-term study involving over 2,000 retinoblastoma patients published in 2021 contradicted this finding [10].

Furthermore, BC was found associated with Costello syndrome, developed through activating germ-line mutations of H-RAS, have developed at a very young age. The youngest experienced treatment failure twice before turning 15 years old, indicating a potential genetic link [11].

Families with Lynch syndrome, particularly those with MSH2 mutations, have an increased risk of UC. The need for regular screening in individuals with these mutations is a topic of ongoing discussion [12].

Next-generation sequencing (NGS) technology has revolutionized large-scale analyses in cancer research, offering unprecedented insights. The initial focus is on MIBC due to its clinical impact and poor survival rates. Recent studies on MIBC have utilized large datasets like The Cancer Genome Atlas (TCGA), Beijing Genomics Institute, MD Anderson, and others to enhance our knowledge of genomic alterations [13].

Analysis of the TCGA dataset revealed alterations in various pathways beyond cell cycle regulation in cancer development. FGFR3 mutations were found in 19% of cases, more prevalent in earlier disease stage, aligning with its link with improved survival outcome in MIBC. EGFR family genes like HER2 and EGFR are often overexpressed in CIS and metastatic cases. Activation of EGFRs triggers PI3K/AKT/mTOR and RAS/MAPK pathways, leading to the expression of onco-genes like MYC and CCND1, as well as migration/invasion regulators like COX2 and MMPs. HER2 amplification is associated lymph node involvements and with EGFR over-expression are linked to increased recurrence and progression risk. In contrast, ERBB3 over-expression is associated with low-grade NMIBC and a favorable prognosis outcome [14].

Sequencing studies have identified more than two dozen genetic variants that increase the risk of BC, accounting for approximately 12% of familial risk. The variations are found in genes related to carcinogen metabolism (NAT2, GSTM1, and UGT1A6), cell cycle control (TP63, FGFR3, and MYC), DNA repair (XRCC1, XRCC2, ERCC3, ERCC4, ERCC5, and NBN), telomere maintenance, and other cellular processes, particularly in high grade cases [15].

Gene-environment interactions have been found between genetic variants and cigarette smoke exposure in BC. These variants expand our understanding of the disease's causes, with some suggesting the use of polygenic risk scores for identifying high-risk individuals. However, the predictive ability of these scores relies on including numerous genetic variants due to their small individual effects. The significance of low-penetrance genetic risk variants for public health remains uncertain. Familial clustering of BC is limited, with few families having more than two first-degree relatives affected. This suggests that widespread germline counseling and testing for all patients may not be cost-effective in identifying high-risk relatives [16].

Molecular Classification &Existing Understanding of MIBC:

Multiple studies have identified at least five distinct subtypes, with a primary division between " squamous / basal -like" and "luminal" subtypes. Efforts are underway to establish a harmony classification scheme for these subtypes [17] (Figure 2 MIBC).

The Ba/Sq subtype, the commonest; 35%, is characterized by squamous and basal differentiation. These tumors exhibit both stem cell and basal markers like KRT1, 4KRT5/6, and CD44. They show HIF1A elevation, STAT3 activation, and urothelial differentiation genes down-regulation. TP53 mutations are frequent (61%) and associated with advanced stages. RB1 mutations are present in 25% of cases, with 14% showing co-occurrence with TP53 mutations. While RB1 and TP53 dual loss is necessary for invasion in BC, other mutations contribute to the invasive potential [18].

The Ba/Sq subtype, subtype of claudin-low not included in the classification, exhibits over-expression of EMT-promoting transcription factors, leading to a mesenchymal signature and poor survival. Unlike Ba/Sq tumors, claudin-low tumors have distinct responses to NAC, but they share similarities with the Ba/Sq-infiltrate subtype, expressing EGFR and CDH3 but not ERBB3 or ERBB2. Both subtypes have higher immune infiltration and features of the stroma-rich subtype [19].

Luminal-like tumors (LumNS, LumP, and LumU) have a papillary morphology and express luminal markers as UPK1A, KRT20, and UPK2. Luminal MIBC shows gene expression signatures of PPARG, ESR2, FOXA1, and GATA3. The three luminal subtypes have different oncogenic mechanisms and mutation statuses, explaining the varying outcome and suggesting diverse pathways to invasion beyond the PAP pathway. Further research on cellular mechanisms can clarify these unique progression pathways [20].

The LumP subtype, accounting for 24% of cases, has the best OS among luminal subtypes due to high FGFR3 activity from gene mutation, fusion, or amplification. FGFR3 overexpression and activating mutations are linked to low-grade Ta. Moreover, it is akin to the Urothelial-like subtype (Uro B and Uro A) and is matched with class I NMIBC luminal-like. Uro B tumors, predominant in MIBC, are considered advanced Uro A tumors, similar to LumP tumors evolving from T1/Ta tumors [21].

When compared to other luminal subtypes, the LumU subtype is linked to lower OS. With a high load of APOBEC-induced mutations, it is the most unstable genomically subtype among the other subtypes. It has more cell cycle activity with increased activity in TP53 and ERCC2 mutations, and is associated with HER2 over-expression. The majority of cases with mutated p53 are high grade, indicating potential for invasion. LumU tumors are with mutations featured of the non-papillary pathway, suggesting they may arise from Class II NMIBCs through this pathway. It is important to distinguish LumP and LumU tumors due to their distinct genomic properties and pathways of progression [22].

The LumNS subtype, a minor fraction of tumors (8%), is a non-specified luminal subtype with immune and stromal infiltration. It has many mutations like PPARG and ELF3 and is associated with the poor OS [23].

The stroma-rich subtype, characterized by more infiltration of both cells immune and stromal, exhibits various cell types of gene signature. Both stroma-rich and LumNS subtypes lack clear definition and may be artifacts of the analysis, therefore, both subtypes constitute a diverse group of tumors cells that require further investigation. The stroma-rich subtype, with a high stromal cell, may be biologically unique from Ba/Sq tumors [24].

The NET-like subtype is infrequent form, accounting for only 3% of cases. They exhibit NET histology and differentiation markers such as, chromogranin A, synaptophysin, and NSE or CD56, along with increased cell cycle activity and concurrent RB1 and TP53 alterations. These patients with both RB1 and TP53alterations have a tendency for advanced disease and poorer OS compared to those with only one of these mutations. NET-like BC include large cell carcinoma and small cell carcinoma, with the last being extremely rare, comprising only 0.5% and typically at advanced stages [25].

Molecular Classification &Existing Understanding of NMIBC:

While MIBC was the main focus at first, there is currently a growing interest in comprehending the genomic landscape of NMIBC, which accounts for 75% of cases of the disease. NMIBC has gained more attention recently as it is considered as a potentially curable disease.

Research into the genomics of NMIBC has been limited despite being the most common form of BC. Early studies faced challenges due to few mutational pathways with low mutational burden. NGS analyses have shown that mutations of FGFR3 are prevalent in NMIBC, particularly in low-grade and stage

disease. A comprehensive NGS study by **Pietzak et al.** in 2017 characterized NMIBC tumors from 105 patients, revealing common mutations like chromatin-modifying gene changes and TERT promoter mutations across all stages and grades. Some mutations were specific to certain grades and stages, such as FGFR3or ERBB2 alterations in NMIBC high-grade [26].

The group at the University of Toronto developed NGS using archival FFPE NMIBC specimens. They identified three unique molecular subtypes of NMIBC—molecular grade risk index (MGRI). MGRI1 characterized by low-grade, while MIBC grouped with MGRI3 NMIBC specimens. MGRI independently predicted progression to MIBC and the PFS [5].

RNA-sequencing has identified molecular grades in NMIBC, which do not align perfectly with MIBC grading system, underscoring the distinct nature of NMIBC and its progression to MIBC. Two significant RNA-seq NGS datasets emphasized on NMIBC have been reported. **Hedegaard et al.** analyzed 460 NMIBC specimens in early-stage and recognized three biologic grades. Grade 1 tumors were lower grade and stage, with lower EORTC risk scores and a lower probability of progression to MIBC. Grade 2-3 tumors were more aggressive, with higher EORTC scores and poor PFS outcomes, indicating a more risk of MIBC progression. Their molecular classes showed overlap with the Lund classification for MIBC, with luminal-like characteristics in classes 1 and 2 and basal-like characteristics in class 3. Mutational signatures and commonly genes mutations in class 2 NMIBC were similar to MIBC, with mutations in MAPK/ERK, ERBB family genes, and DDR associated with class 2 tumors [27].

Hurst et al. identified NMIBC subtypes with unique gender and metabolic biases, as well as variations in the frequency of KDM6A mutations. One subtype showed loss of 9q, including increased Ki67, TSC1, DNA repair, mTORC1 signaling, and upregulated glycolysis, even in primary pTa NMIBC [28] (Figure 3).

Impact on treatment therapy:

Early, genomic studies have identified mutations with clinical significance and viable treatment targets in 69% of tumors. Clinical trials are already leveraging these findings, such as evaluating the response of ERBB2 and ERCC2 mutated tumors to cisplatin based CTH in MIBC [29].

Molecular subtyping has improved our knowledge of MIBC, helping predict responses to therapy. The squamous / basal -like subtype is linked to aggressive disease behavior, on the other hand, the luminal subtype is less aggressive with better survival outcome. Studies have shown different responses to CTH based on molecular subtypes, with luminal subtype having better outcomes even receiving CTH. Basal MIBC patients show significant clinical improvement with CTH [30].

NAC induces molecular alterations in MIBC, leading to divergent responses and changes in tumor behavior and subtype. Basal tumors are recommended for NAC instead of RT due to their hypoxic effect. RT is less used and mainly used for palliative care, with potential benefits for tumors expressing genes associated with T-cell activation and INFγ signaling. Immunotherapy response is not clearly linked to the subtypes proposed in the consensus classification, but CD8+ T cell infiltration in claudin-low and luminal-infiltrate tumors may indicate a positive response to ICTs [22].

LumP tumors are less likely to respond to cisplatin-based NAC compared to basal tumors. Some luminal types (p53-like subtype) with WT TP53 expression are refractory to CTH, possibly due to p53-induced reversible senescence impairing the response to apoptosis post-DNA damage. The role of p53-signature in NAC response in BC remains unclear. MDM2 alteration is indicative to inactivate p53 in MIBC (76%). Further research is needed to understand CTH refractory mechanisms in this subset of luminal types [31].

NET-like and LumU tumors may benefit from immunotherapy, while stroma-rich tumors may be resistant. EGFR-targeted therapies show promise in Ba/Sq tumors, but resistance mechanisms need further investigation. HER2 targeting in MIBC has not been successful, possibly due to patient selection methods. LumP tumors with FGFR3 over-expression may benefit from FGFR inhibitors, such as erdafitinib, especially in cases resistant to cisplatin-based NAC [13, 25].

The significance of mutational burden in BC cannot be underestimated, especially with the growing interest in ICIs that help the immune system target tumors. Five ICIs had been approved for metastatic/advanced BC, with ongoing trials in MIBC. Pembrolizumab stands out as the first FDA-approved drug based on MSI-H or dMMR, which aligns with higher burgen of mutations burden in many patients [32].

DNA damage repair (DDR) gene alterations, important for therapy decisions, were found in a significant proportion of high-grade NMIBC tumors, similar to MIBC. ARID1A mutations were linked with a more risk of recurrence after intravesical BCG therapy. The study highlighted numerous potential therapeutic targets in NMIBC [26].

Erdafitinib, a small molecule inhibitor of fibroblast growth factor receptor (FGFR), has FDA approval on 19 January 2024 for treating patients with metastatic or locally advanced BC that have FGFR3 or FGFR2 alterations and have progressed after cisplatinum-containing CTH. This approval based on the positive outcomes from the THOR study, demonstrating improved OS, PFS, and ORR compared to CTH [33].

We may select patients more effectively for systemic treatments like ICIs or CTH, pending agreement on classification and findings from clinical trials. Molecular classification is still not a reliable enough basis for clinical decisions, even though some centers use it in the absence of solid evidence. One of the challenges with tumor heterogeneity is the in-depth analysis of molecular diversity that is being researched [31].

Further research is needed to understand the value of many types of heterogeneity of the tumor, including rare ones, tumor evolution and treatment response.

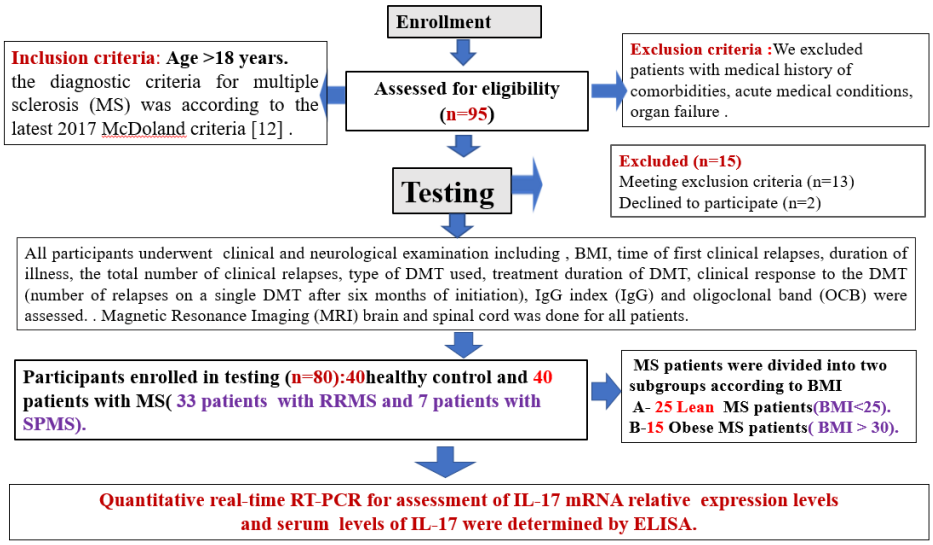

Figure 1: flow chart of the study

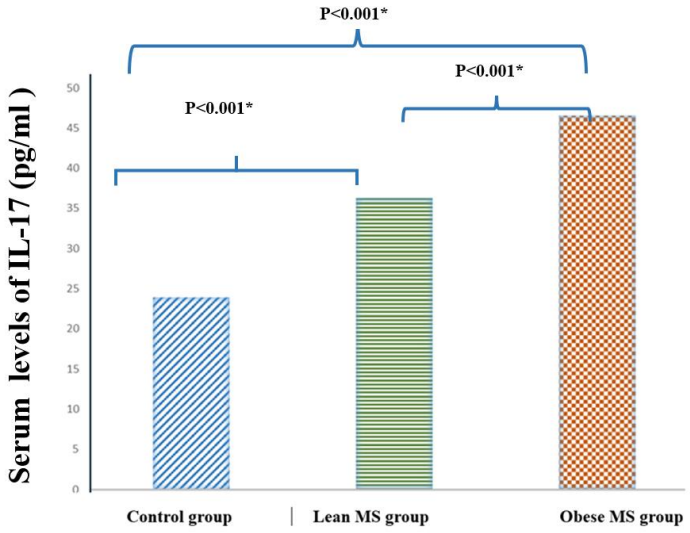

Figure 2A: comparison between studied patients regards serum IL-17(pg/ml)

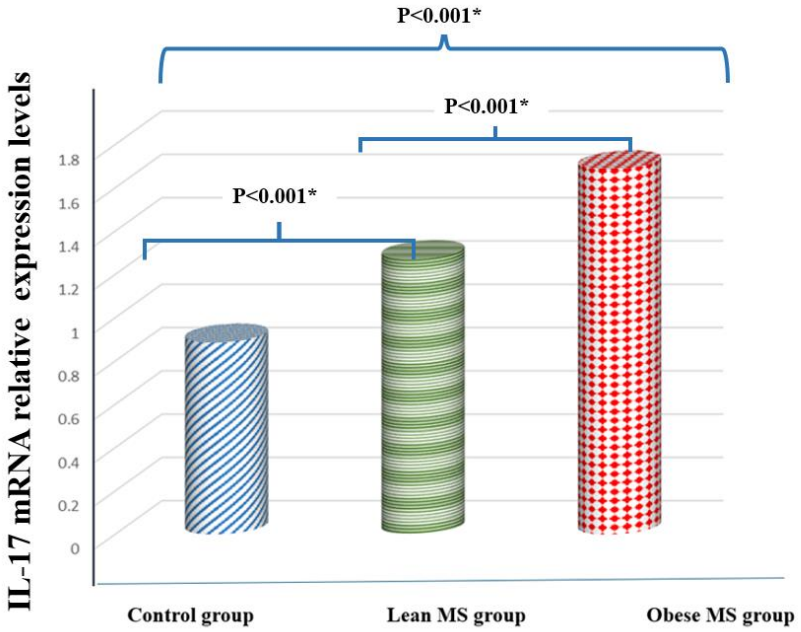

Figure 2B: comparison between studied patients regards IL-17 mRNA relative expression levels.

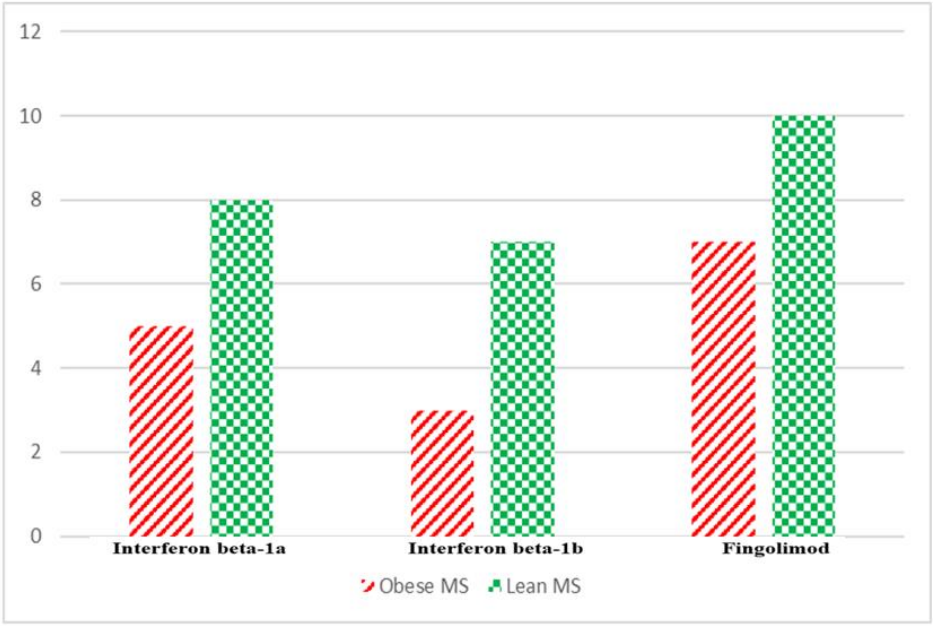

Figure 3: comparison between lean and obese patients regards DM

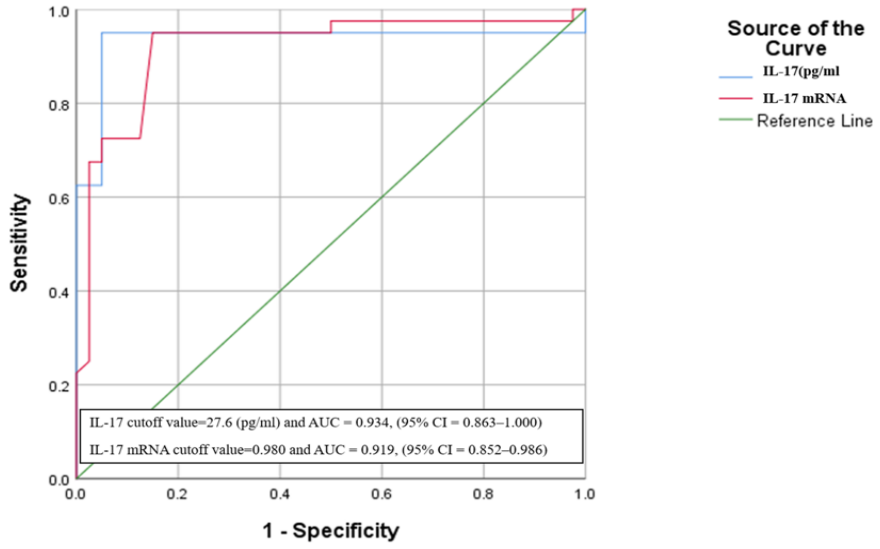

Figure 4 A: ROC curve of IL-17(pg/ml) and IL-17 mRNA levels for differentiation of patients with MS among participants.

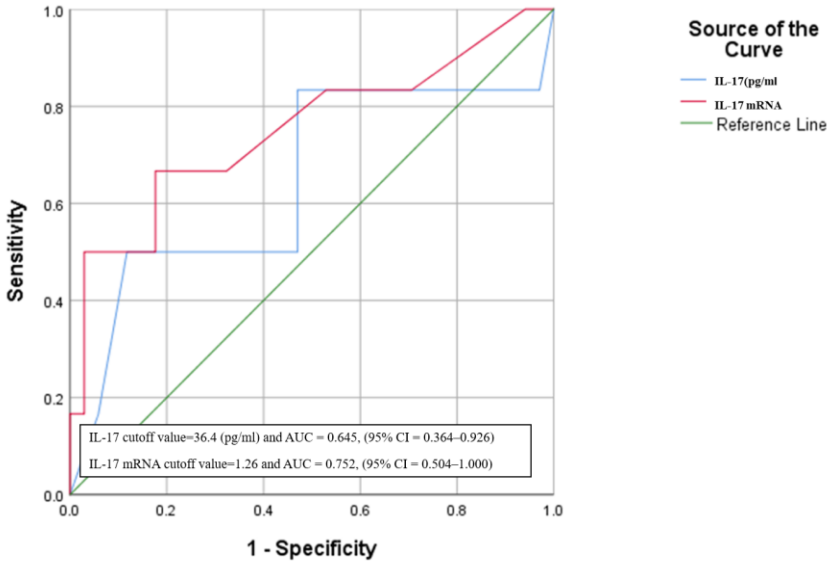

Figure 4 B: ROC curve of IL-17(pg/ml) and IL-17 mRNA levels for differentiation of patients with obesity among MS patients.

Limitations

Recent studies on molecular research of BC cohorts have identified distinct molecular classes among patients, primarily based on untreated tumor samples. However, the heterogeneity of BC, both within and between tumors, poses challenges to this classification. Tumors can exhibit many subtypes gaining the same tumor, making it difficult for a single molecular subtype to identify the entire tumor. While molecular classification of BC is gaining acceptance, standardization and consensus are still lacking for clinical implementation. Factors such as cellular infiltration, content, gene selection, profiling techniques, and antibody selection for IHC need to be defined for accurate subtyping.

Genetically engineering can elucidate the role of unique alternations in different subtypes and shed light on subtype evolution. While personalized treatment approaches are valuable, the need for grouping patients for clinical studies remains crucial.

CONCLUSIONS

Comparisons between MIBC and NMIBC cohorts revealed an overlap in tumor mutational landscape,

indicating that some NMIBC cases evolve to MIBC. For instance, FGFR3 mutations, common in NMIBC, are also present in 10-20% of MIBC specimens.

The molecular distinctions between MIBC and NMIBC are not well understood. A clearer understanding of their relationship is crucial for a molecular-based clinical classification. Understanding the molecular mechanisms of UC tumor evolution is a key [13].

Genomic and transcriptomic analyses of BC have recognized a unique molecular alteration in MIBC and non-invasive papillary tumors low-grade, and also matching between MIBC and NMIBC high-grade types. High-grade NMIBCs share complex copy number alterations and accumulate genomic instability similar to MIBCs, indicating a progression from low-grade Ta tumors. Mutations in DNA repair / replication genes with tumor suppressors are common in MIBC and papillary tumors high-grade, suggesting a convergence of pathways in acquiring invasive potential. This suggests that high-grade NMIBC can progress to MIBC [18, 19].

Two main carcinogenic pathways have been proposed: the papillary pathway leading to NMIBC low-grade from hyperplasia, and the non-papillary pathway leading to MIBC from CIS or dysplasia. NMIBC High-grade may arise from a combination of dysplasia and hyperplasia, indicating an intersection of the two pathways [20].

On the basis of available information, individualized patient services is being sought after. For instance, the Decipher® Bladder Cancer Classifier has been developed to classify patients into specific molecular subtypes, aiding in treatment decisions. Prospective trials using biomarkers from this test will validate its utility.

Novel therapies, including ICIs, are being studied in the perioperative setting. Response rates to these inhibitors are comparable to chemotherapy, but many patients do not benefit. Improved patient selection and understanding of resistance mechanisms are needed [34].

While these data have enhanced our knowledge of disease pathophysiology, they have not led to significant alterations in BC management. Recent discoveries may have a greater impact in this regard. Our study can be a valuable resource for advancing biological discoveries and developing therapies for UC in the future.

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