MYBL2 GENE AS PROGNOSTIC BIOMARKER IN BREAST CANCER: A SYSTEMATIC REVIEW

ABSTRACT

Breast cancer is a relevant public health problem, either because of its high incidence or because of mortality rates. There are several forms of classification of the pathology, so that it is demonstrated, currently, the direct influence of genetic aspects on the clinic of affected patients. In this sense, new genetic biomarkers have been sought to directly impact the understanding of the disease, as well as having prognostic value, being the MYBL2 gene important in this context. **Aim:** Thus, the present study aimed to identify and select evidence about the MYBL2 gene as a prognostic biomarker of the disease. Following PRISMA Statement 2020 guidelines, a systematic search was conducted in electronic databases such as PubMed and Science Direct to identify studies evaluating MYBL2 as a prognostic genetic biomarker in breast cancer. A narrative synthesis was used to analyze and synthesize findings, according to established inclusion and exclusion criteria. There were 122 related publications, 12 of which were selected to be evaluated for eligibility in full text, so that 5 articles were selected for the qualitative synthesis of this study. The findings demonstrate the role of MYBL2 as a potential prognostic biomarker for breast cancer, and overexpression of this gene is an indicator of worse prognosis. However, more clinical studies are needed, mainly to evaluate the MYBL2 gene exclusively, and not only together with other potential biomarker genes.

Keywords: *MYBL2 gene; breast cancer; biomarker; prognosis; health.*

1. INTRODUCTION

Worldwide, breast cancer (BC) is the most common cancer in women and the second most common cancer that leads to death [1], with an incredible 600,000 deaths per year [2]. Currently, the treatment of choice is decided by clinical and histopathological factors, such as tumor size and stage, lymph node conditions and estrogen receptor status, although these elements have some limitations for prognostic determination [3].

Although these conventional principles of prognosis are still indispensable factors for determining survival over a long period, it has been attested that the understanding of progression, prognosis and susceptibility to disease can be influenced by genetic factors [4]. Several independent prognostic factors exert influence on the overall survival (OS) rate in patients [5,6], namely: tumor size, local lymph node involvement, proliferation rate, tumor cell differentiation and patient age [7,8]. Moreover, the diagnostic stage presents significant changes in patient survival: diagnosis at stage 1 results in a 90% 5-year survival rate, while at stage 4 this rate drops to 20% [9]. The initial tumor classification also plays a crucial role in patient OS [10]. The mutational subtype of the tumor, classified as luminal A, luminal B, HER2-enriched or triple negative breast cancer (TNBC), also plays an important role.

HER2-enriched and TNBC subtypes are the most aggressive, showing a lower 4-year survival rate compared to luminal subtypes [11, 12, 13].

There are records that the determination of biomarkers that inform resistance, recurrence and occurrence of metastases will be a predictor of deliberations regarding treatment and foreshadowing of patient survival [14, 15]. In this context, overall survival (OS) rates have been increasing in luminal phenotypes, due to the use of targeted therapies for tumors that are estrogen receptor positive [16]. However, acquired, and intrinsic resistance to treatment remains a complication, and unfortunately, many breast cancer (BC) patients develop resistance to the main chemotherapeutic agents used [14, 16].

MYBL2 gene overexpression is common and characterizes a deleterious prognostic biomarker in several types of cancer, including breast cancer [18], precisely because it is linked to high replicative instability and tumor irruption, by delineating the immune microenvironment and stimulating the epithelial-mesenchymal transition [19]. This gene is an important predictive factor for the presentation of metastases, resistance, and relapse of CM [2].

Thus, the objective of the present study was the identification, selection, and synthesis of relevant evidence regarding the MYLBL2 gene as a prognostic biomarker of the disease.

2. METHODS

The present review aimed to identify, select and synthesize the relevant evidence available in the literature on the aforementioned topic, based on clear selection and eligibility criteria. In this sense, this systematic review followed the PRISMA guidelines and used the PICOS strategy to elucidate the relationship between the MYBL2 gene in breast cancer, as a potential prognostic gene [20].

The search was based on scientific evidence available in the PubMed and Science Direct databases, using the MeSH terminology (Medical Subject Headings). The following search strategy was used: "MYBL2" AND "breast cancer" AND "prognostic". Additional filters were used, such as English language and type of document (article), with no year restriction. The studies were pre-selected by reading their titles and abstracts for further analysis and data extraction.

All papers found were analyzed for eligibility according to the following criteria: (i) correlation between alterations in the MYBL2 gene and breast cancer prognosis, (ii) papers with complete data and statistical results of correlation between alterations in the gene of interest in breast cancer and (iii) original studies. The following publications were excluded from the present review: letters, case reports, reviews and meta-analyses, conference abstracts, studies related to other types of pathologies and method validation studies. The study selection process was conducted in two phases, with two reviewers independently reviewing all titles and abstracts obtained in the searches. References considered to be 'potentially eligible' proceeded to the second phase, which consisted of full-text assessment to confirm their eligibility. A third reviewer resolved any dissent. Due to the review approach adopted in this work, there was no need to submit to or obtain approval from a research ethics committee.

3. RESULTS

The study selection process for this systematic review followed the PRISMA guidelines [20], with the intention of identifying relevant literature regarding the MYLBL2 gene as a prognostic biomarker of the disease. the database search resulted in the identification of a total of 122 publications. 12 articles were selected to be assessed for full-text eligibility. During the screening phase, the titles, and abstracts of the 12 medical records were carefully examined, leading to the exclusion of 7 articles for not meeting the pre-established eligibility criteria. Therefore, 5 articles remained and were included for the construction of the qualitative synthesis of the present work, which provided valuable information to the proposed theme (Fig.1).

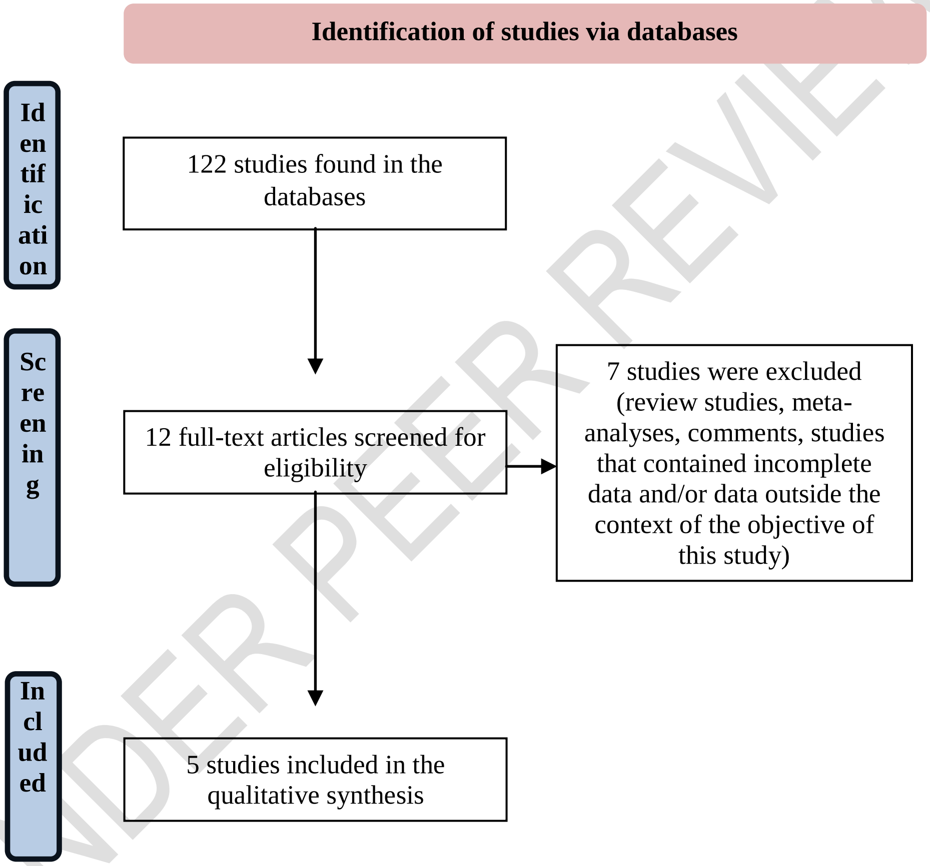

Fig.1. PRISMA flowchart depicting the study selection process.

Thus, the sample of this study was composed of 5 original studies, published between 2011 and 2023, made with data from 5 countries - Sweden, Poland, China and Spain. As for the treatment of each of the selected studies, Table 1 illustrates data such as the reference, study objective, main findings and conclusions.

Authors	**Aims**	**Results**	**Conclusions**

Shi *et al.* (2011)	To evaluate the effect of 12 functional SNPs and 8 tag-SNPs of the 20q13 amplicon genes MYBL2, AURKA, ZNF217, STK4 and PTPN1 on CM risk and impact on clinical outcome.	Increased susceptibility to CM associated with 3 polymorphisms in MYBL2 (rs619289, rs826943 and rs826944), 2 polymorphisms in AURKA (rs6064389 and rs16979877) and 1 30 UTR polymorphism in ZNF217 (rs1056948).	Genes such as MYBL2 may be important prognostic indicators, as they affect hormone receptor status in breast tumors and influence tumor aggressiveness and patient survival.
Shi *et al.* (2011)	To evaluate the effect of 6 SNPs of E2F1, E2F3 and E2F4 and 22 SNPs of nine genes regulated by MYBL2, BCL2, BIRC5, COL1A1, COL1A2, COL5A2, ERBB2, CLU, LIN9 and TOP2A on CM risk and clinical outcome.	Worse survival in carriers of SNPs rs8073069 and rs1042489, with multivariate analysis supporting the role of rs8073069 as an independent prognostic marker; occurrence of hormone receptor positive tumors in carriers of rs1564483; occurrence of stage II-IV tumors and histological grade 3 in carriers of rs4987852; propensity to occurrence of regional lymph node metastases and stages II-IV in carriers of SNP rs9331888.	MYBL2 variants (BIRC5, BCL2 and CLU, essentially) can be used as progression and prognostic markers for CM.
Shao *et al.* (2018)	To identify key genes, pathways and prognostic values related to ER and HER2 negative breast cancer.	355 DEGs were identified: 140 up-regulated and 215 down-regulated genes. High expression of MYBL2, as well as CCNE1 and KRT16, was associated with worse relapse-free survival and overall survival in ER-negative/HER2-negative BC.	MYBL2 overexpression directly related to worse prognosis.
Xin *et al.* (2021)	To investigate whether elevated MYBL2 expression could be used as a prognostic and predictive factor in a variety of human cancers, including breast cancer.	MYBL2 may be a significant prognostic marker in BRCA-mutated patients, where the triple-negative subtype and the Her2-positive group, with high MYBL2 expression, have worse prognosis. Overexpressed MYBL2 is correlated with PAM50 subtypes of breast cancer.	Elevated MYBL2 expression represents a significant prognostic biomarker, especially for BC Moreover, patients with P53 mutation and elevated MYBL2 expression showed worse survival in altered BRCA.
García-Torralba *et al.* (2023)	Prediction of MYBL2, NLR, TILs and AURKA when associated with immune response and cell proliferation combined with clinical parameters.	MYBL2, NLR, TILs and AURKA showed prognostic value for overall survival in univariate analysis and in patients with hormone receptor status, HER2 and response to neoadjuvant chemotherapy in multivariate analyses.	The use of genes such as MYBL2 as biomarkers tends to progressively increase their survival discriminatory capacity.

ER: estrogen receptor, HER2: human epidermal growth factor 2, DEGs: differentially expressed genes. **Table 1**. Data extracted from the selected studies.

DISCUSSION

Considering that breast cancer has the highest global incidence and represents the leading cause of cancer death in women worldwide [1], the search for reliable prognostic biomarkers is essential to enable better stratification of patients. Thus, the present review focused on the search for studies that evaluated the prognostic value of alterations in the MYBL2 gene in patients with breast cancer, since it is a master gene for cell cycle regulation[3]. The following are studies that suggest the prognostic value in the evaluation of this gene regarding the susceptibility to occurrence of BC, survival of patients with specific subtypes of BC, its role in the interaction with other markers already described in the prognosis of BC and determination of better treatment options for each type of patient.

Shi et al. (2011) [4] investigated genetic variation in five 20q13 amplicon genes (MYBL2, AURKA, ZNF217, STK4 and PTPN1), to demonstrate their impact on breast cancer susceptibility and clinical outcome. In this regard, the association of 3 polymorphisms in MYBL2 (rs619289, rs826943 and rs826944) with the highest risk for breast cancer development in the Swedish population was demonstrated. In contrast to this finding, in the Polish population, according to the present study, SNPs rs619289 and rs826944 did not show an association with increased susceptibility to breast cancer. The partial discordance of the results was possibly attributed to the different etiologies of familial/early-onset breast cancer compared to non-familial. In addition, minimal allelic difference was observed for the SNP MYBL2 rs619289 between the different populations. It was further suggested that the partially divergent results may be a chance outcome. Despite the partial divergence of the results between the Swedish and Polish populations in the study it was possible to conclude that genes such as MYBL2 influence the survival of patients with BC.

Genetic mutations that result in a clinical phenotype broaden the understanding of which protein regions are vital for the pathophysiology of human diseases. While MYBL2 is generally overexpressed in CM, mutations in its coding and promoter regions have also been identified and associated with such events. In this sense, the work of Shi et al. (2011) [21] demonstrated an association of increased susceptibility to CM related to 3 polymorphisms in MYBL2 (rs619289, rs826943 and rs826944). Likewise, single nucleotide polymorphisms (SNPs) present in the regulatory region of MYBL2 may increase susceptibility to CM, when compared to wild-type MYBL2, as demonstrated by another work by Shi et al. (2011)[4], also included in the present study. Thus, the SNPs described are all located in established MYBL2 promoter regions, which may affect transcription factor binding and therefore alter expression levels. These SNPs may also allow different transcription factors to bind to MYBL2, leading to increased expression; however, this needs to be further investigated in a clinical setting.

According to Shao et al. (2018) [22] there is a relationship between hormone receptor-positive BC and overexpressed genes such as MYBL2. According to the authors, high MYBL2 expression is associated with a worse overall survival rate and relapse-free survival in ER-negative/HER2-negative BC. The study also points out that MYBL2 is associated with cell cycle progression and that the process of tumorigenesis and chromosomal instability may be caused by an overexpression of this gene, demonstrating its potential as a prognostic biomarker.

This relationship of MYBL2 with the process of cell proliferation and carcinogenesis is also demonstrated in the article by Xin et al. (2021) [18], which further emphasizes the relationship of MYBL2 overexpression with worse prognosis and pathophysiological features of breast cancer and other cancers such as colorectal cancer, lung cancer, sarcoma, and neuroblastoma. Thus, these findings contributed to the conclusion in the study that high MYBL2 expression can serve as a diagnostic marker between normal and tumor tissue in most cancer types in humans. In addition to being indicative of worse prognosis with worse overall survival rates, disease specific survival, progressive free interval, confirming a worse prognosis in patients with high MYBL2 levels. The study in question also correlates MYBL2 overexpression with altered p53 signaling and points out that E2F1, E2F2, E2F7 and ZNF659 may interact directly or indirectly with the MYBL2 promoter, which may explain its altered levels.

Finally, the work of García-Torralba et al. (2023) [19] demonstrates, in uni and multivariate analysis, the potential of MYBL2 and other genes (NLR, TILs and AURKA) as prognostic and predictors against neoadjuvant chemotherapy (NCT). In view of the exploratory and predictive analyses performed by the authors, it was concluded that the analysis of gene expression, added to the expression of hormone receptors and HER2 status, allowed a better stratification of the risk of events in the analyzed cohort. Given that current research points to MYBL2 as a valuable indicator of disease severity and treatment response in BC, the identification, characterization and understanding of this gene may elucidate mechanisms and contribute to the development of more specific and effective therapies.

4. CONCLUSION

After evaluating the studies included in the present review, it is evident that the MYBL2 gene has prognostic value in BC, and the evaluation of its expression in this scenario is valid. However, the present study presented limitations, since studies describing the MYBL2 gene with prognostic value were sought, the present work describes the studies that approached it in this way. In this sense, there is mainly prognostic value of the gene in association with others, such as those included in the present study, and no studies were found that evaluated it in isolation. Therefore, clinical studies evaluating the gene in question, especially in relation to CM, are necessary to elucidate its prognostic value according to the exclusive expression of this gene.

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