

ASSOCIATION BETWEEN DMD GENE ALTERATIONS AND OVERALL SURVIVAL IN
BREAST INVASIVE CARCINOMA

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ABSTRACT

Breast invasive carcinoma is a heterogeneous malignancy in which several well-established genes, such as BRCA1, BRCA2, and TP53, have undergone extensive study. More recently, the DMD gene, which codes for the protein dystrophin, has gained attention in cancer research because of its proposed tumour-suppressive functions and its association with tumour progression and patient prognosis (Wang et al., 2014; Luce et al., 2017). This study investigated the association between DMD alterations, based on the cBioPortal query function using the prompt "DMD", and overall survival in patients with breast invasive carcinoma. Three TCGA datasets - PanCancer Atlas, Cell 2015, and Firehose Legacy - were analysed using cBioPortal (Cerami et al., 2012; Liu et al., 2018). Patients were divided into DMD-altered and DMD-unaltered groups, and survival outcomes were compared using Kaplan-Meier analysis, log-rank p values, q values, median overall survival, and hazard ratios. Across all three datasets, the altered group showed shorter median overall survival than the unaltered group, with observed differences in median survival ranging from 35.87 to 45.53 months. The datasets also produced log-rank p values below 0.05, although the q value for PanCancer Atlas increased to 0.0958 following cBioPortal's multiple-testing adjustment. The hazard-ratio estimates ranged from 1.862 to 2.029, indicating a consistent direction towards higher mortality hazard in the altered group, despite the wide confidence intervals. These findings suggest that DMD alterations may be associated with poorer overall survival in patients with breast invasive carcinoma. However, the small altered patient population, possible overlap among the TCGA datasets, and statistical uncertainty indicate that these findings should be interpreted with caution. Furthermore, larger datasets and multivariable survival models are required to determine whether DMD alterations can reliably predict prognosis in patients with breast invasive carcinoma.

INTRODUCTION

Breast invasive carcinoma is a heterogeneous disease, with 2.3-2.4 million cases diagnosed each year and roughly 670-694 thousand fatalities per year (World Health Organisation, 2026). It is characterised by malignant cells that invade beyond the ducts and lobules into surrounding breast tissue. Although well-established genes associated with the disease, such as BRCA1, BRCA2, and TP53, have been extensively studied (Shiovitz & Korde, 2015), the contribution of unconventional genes and their tumorigenic behaviour remains an important area of research and investigation.

The DMD (Duchenne Muscular Dystrophy) gene is located on the X chromosome and codes for a protein called dystrophin, a large cytoskeletal protein mainly

involved in maintaining myocyte stability (Jones et al., 2021).

More recently, DMD has also gained attention in cancer research, with multiple studies reporting the effects of certain mutations in the gene on cancer progression and patient outcomes (Luce et al., 2017). Dystrophin has also been linked to tumour-suppressive functions involved in the maintenance of cellular structure and control of invasive behaviour (Wang et al., 2014).

In breast invasive carcinoma, DMD alterations have been identified in multiple datasets (Alnassar et al., 2023), but their association with patient prognosis remains unclear compared with that of already well-established breast-cancer-associated genes (Jones et al., 2021). This study

aims to investigate the relationship between DMD alterations and overall survival in patients with breast invasive carcinoma using multiple TCGA datasets

available on cBioPortal. It is theorised that patients with DMD alterations may demonstrate poorer survival rates than those with an unaltered DMD gene.

AIM Evaluate the relationship between DMD alterations and overall survival rates using three TCGA datasets available on cBioPortal.	Alternate Hypothesis (H1) Patients with DMD alterations have different overall survival distributions compared with patients without a DMD alteration; based on previous evidence, the overall survival distribution is expected to be lower in the altered group than in the unaltered group.
Null Hypothesis (H0) There is no difference in the overall survival distribution between patients with altered DMD and those with unaltered DMD.	OBJECTIVE This study aims to extract and compare group sizes, median survival, log-rank p values, q values, and hazard ratios. By assessing consistency across different datasets and differentiating association from causation, a clearer perspective can be gained on the relationship between DMD alterations and the survival distribution of patients with breast invasive carcinoma.

Analysis Method

This study uses three different datasets, namely TCGA Cell 2015, TCGA Firehose Legacy, and TCGA PanCancer Atlas (Liu et al., 2018). cBioPortal (Cerami et al., 2012) was used to analyse the datasets and generate Kaplan-Meier graphs. For each study, patients were classified according to the DMD alteration status returned by cBioPortal following a gene query for "DMD". No new patients were recruited, and no treatment intervention was assigned.

For each dataset, patients were divided into altered and unaltered groups. The alterations should not be described as a single, uniform mutation, nor should it be assumed that every mutation produced an equivalent functional loss. Overall survival was selected as the clinical endpoint of the study.

Comparative Approach

Across the three datasets, results were compared descriptively. Differences in median survival were calculated by finding the difference between the altered and unaltered medians. Alteration prevalence was calculated by dividing altered cases by total evaluable cases. Hazard ratios were not averaged across all three datasets because patients may overlap between datasets.

RESULTS

The three datasets contained 816-1090 evaluable patients. Within these cohorts, only a small but similar percentage of patients was classified in the altered group: 6.64% in PanCancer Atlas, 5.58% in Cell 2015, and 5.69% in Firehose Legacy. Event counts were relatively small in the altered groups.

Table 1: Cohort sizes, altered prevalence, events, and median overall survival values. Source: cBioPortal - PanCancer Atlas, Cell 2015, and Firehose Legacy.

Cohort	Total n	Altered n	Events A/U	Median OS altered	Median OS unaltered	Difference
PanCancer Atlas	1084	72 (6.64%)	14/137	93.83 mo	129.70 mo	35.87 mo
Cell 2015	816	48 (5.88%)	12/107	84.53 mo	129.60 mo	45.07 mo
Firehose Legacy	1090	62 (5.69%)	15/136	84.53 mo	130.06 mo	45.53 mo

In each analysis, the altered group had shorter median survival. PanCancer Atlas showed a median survival of 93.83 months for the altered group and 129.70 months for the unaltered group, a difference of 35.87 months. Cell 2015 showed a median survival of 84.53 months in the altered group and 129.60 months in the unaltered

group, a difference of 45.07 months. Firehose Legacy showed a median survival of 84.53 months in the altered group and 130.06 months in the unaltered group, a difference of 45.53 months. Hence, the observed difference ranged from approximately 3.0-3.8 years.

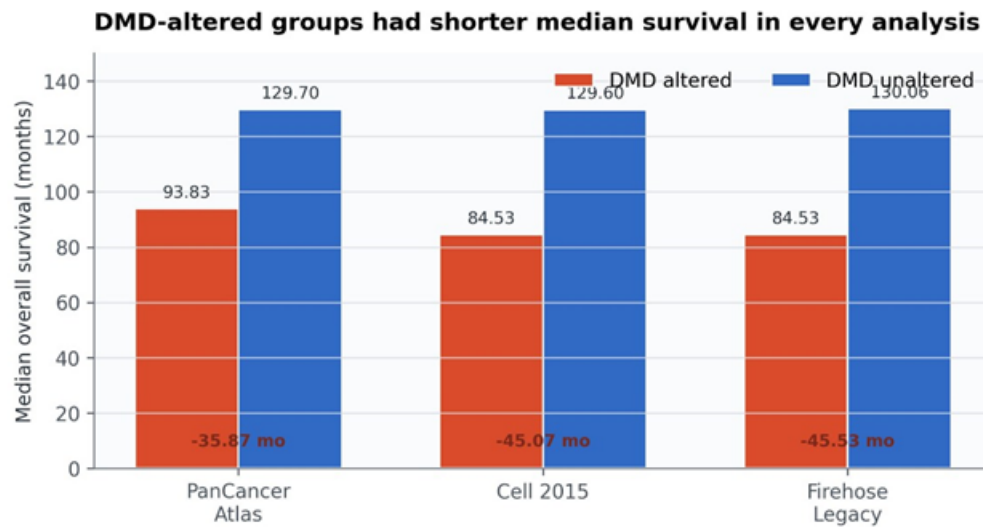


Figure 1: Median overall survival across the three datasets.

TCGA PanCancer Atlas



Figure 2: Kaplan-Meier overall survival curve for TCGA PanCancer Atlas.

TCGA Firehose Legacy

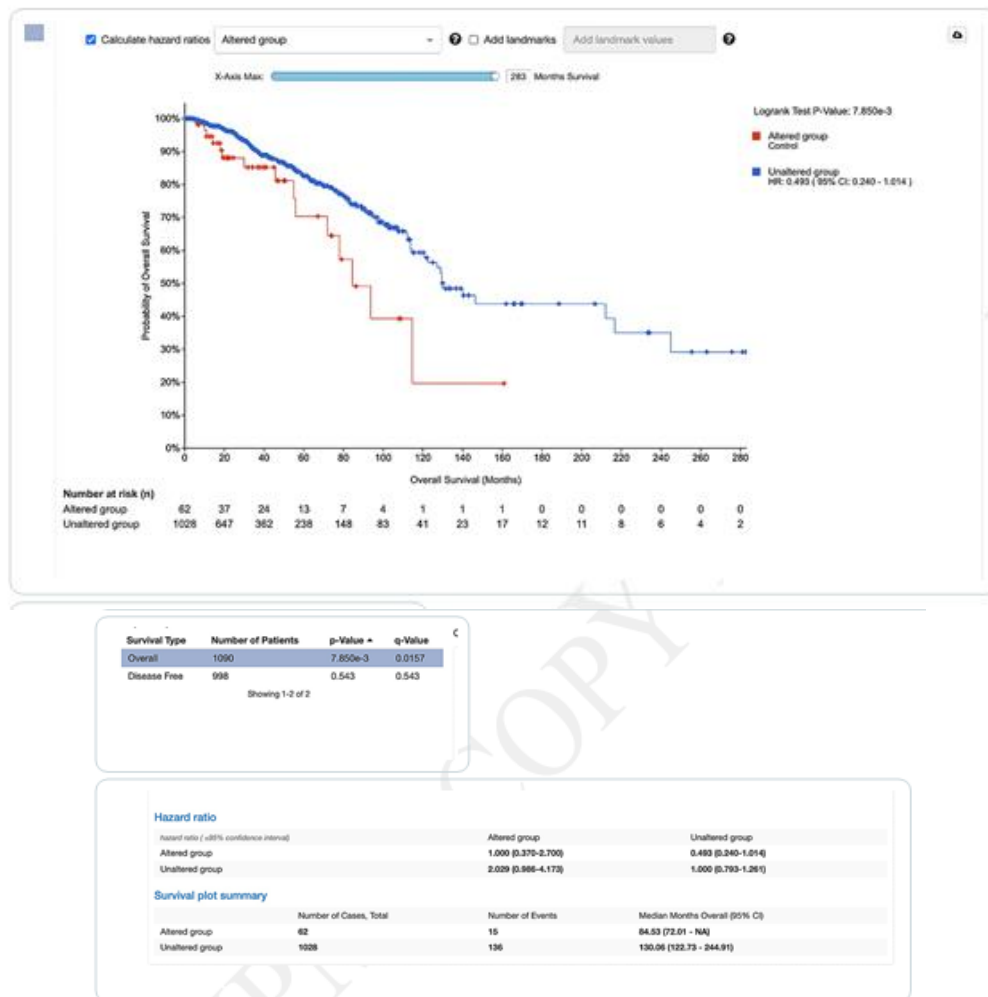
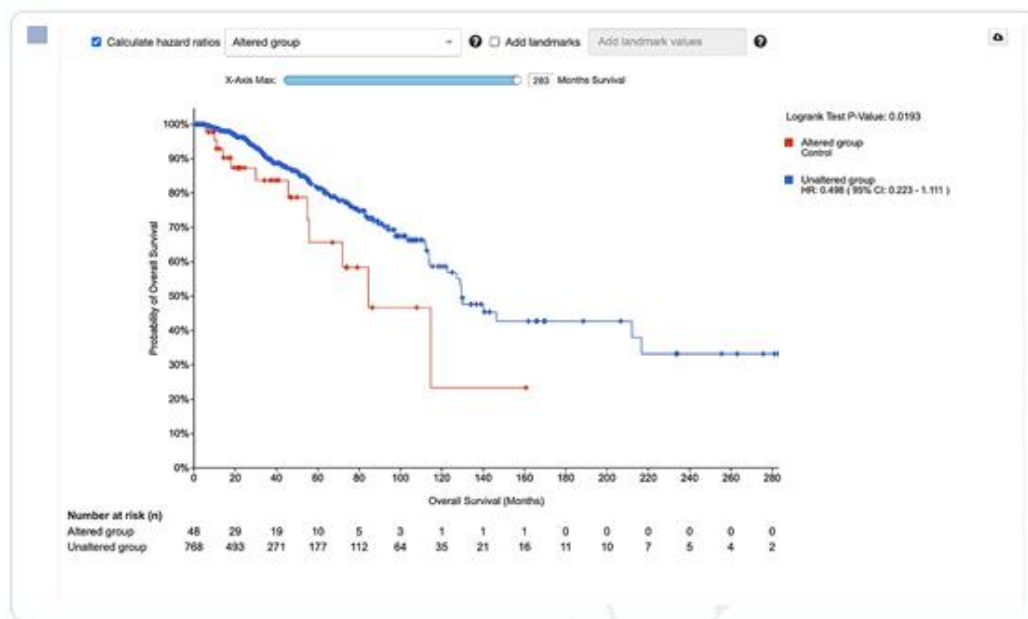


Figure 3: Kaplan-Meier overall survival curve for TCGA Firehose Legacy.

TCGA Cel 2015



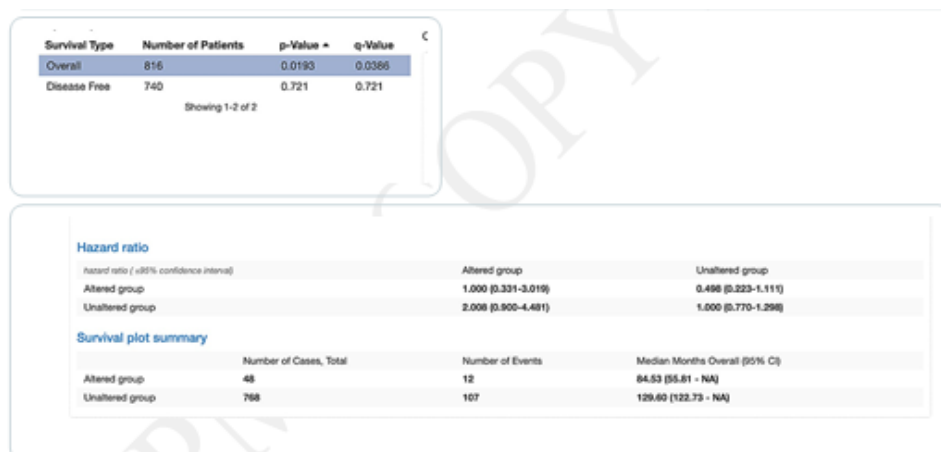


Figure 4: Kaplan-Meier overall survival curve for TCGA Cell 2015.

Overall Comparison

The log-rank p values for all three datasets showed a significant difference between the overall survival distributions of the altered and unaltered groups because all were below 0.05. PanCancer Atlas showed a p value of 0.0240, Cell 2015 showed a p value of 0.0193, and Firehose Legacy showed a p value of 0.00785. After the

portal's multiple-testing adjustment, the q values for Cell 2015 and Firehose Legacy were 0.0386 and 0.0157, respectively, and remained below 0.05. However, the q value for PanCancer Atlas was 0.0958, indicating that this result should be interpreted more carefully after correction for multiple comparison.

Table 2: Summary of hazard ratios, confidence intervals, p values, and q values. Data transcribed from cBioPortal.

Cohort	HR	95% CI	p-value	q-value	Interpretation
PanCancer Atlas	1.862	0.908-3.819	0.0240	0.0958	Nominal p < .05; q >= .05
Cell 2015	2.008	0.900-4.481	0.0193	0.0386	p and q < .05
Firehose Legacy	2.029	0.986-4.173	0.00785	0.0157	p and q < .05

The hazard ratios ranged from 1.862 to 2.029. All three datasets showed a hazard ratio above 1, indicating a consistent direction towards higher mortality hazard in the altered group.

However, the 95% confidence intervals were wide, indicating substantial uncertainty in the exact magnitude of the association.

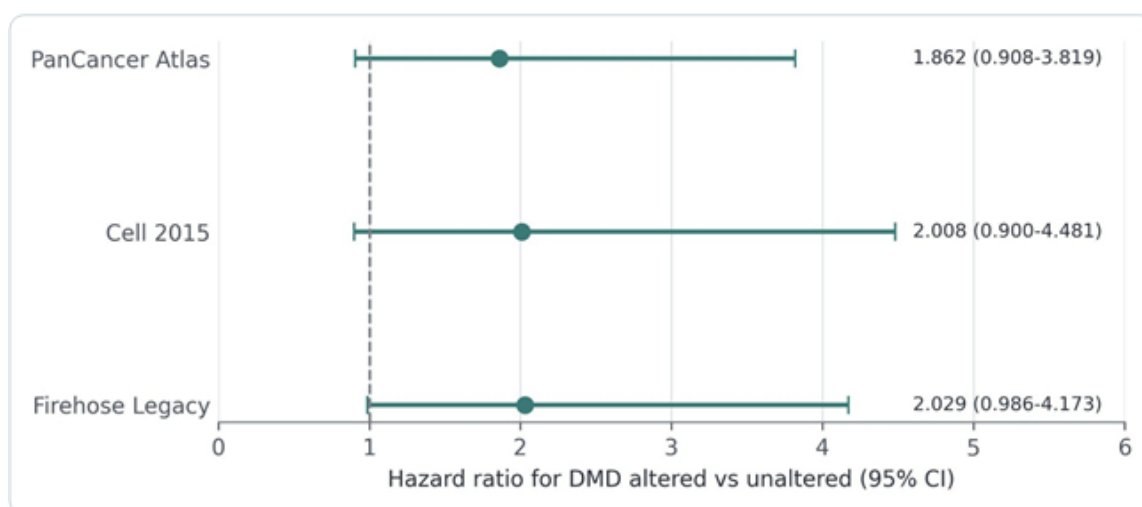


Figure 5: Forest plot of hazard ratios for DMD altered vs unaltered groups (95% CI).

DISCUSSION

Findings: In all three datasets, DMD alterations were consistently associated with poorer overall survival, with the difference in median survival ranging from 35.87 to 45.53 months. This consistency in direction across the three datasets supports the hypothesis that DMD alteration may have prognostic relevance.

The Kaplan-Meier analysis showed log-rank p values below 0.05 in all three datasets, with values of 0.0240 for PanCancer Atlas, 0.0193 for Cell 2015, and 0.00785 for Firehose Legacy. However, after the multiple-testing adjustment applied by cBioPortal, the q value for PanCancer Atlas increased above 0.05 to 0.09583, whereas the q values for Cell 2015 and Firehose Legacy remained below 0.05. This indicates that, despite the overall pattern being consistent, the strength of statistical evidence was not equal across the three datasets. The PanCancer Atlas result should therefore be interpreted more carefully.

Hazard ratios ranged from 1.862 to 2.029, indicating an approximately 86% to 103% higher mortality hazard in DMD-altered patients compared with unaltered patients. However, the 95% confidence intervals were wide and included 1.0 in all three datasets. This indicates that, although the point estimates consistently favoured poorer overall survival in the altered group, the exact magnitude of the association remains uncertain, which may partly reflect the small sample size.

Previous studies support the present findings but also highlight important differences. Alnassar et al. (2023) reported that reduced DMD expression was associated with poorer survival outcomes in several cancers, including breast invasive carcinoma. Studies have also identified DMD alterations across non-myogenic cancers (Luce et al., 2017). These findings are consistent with the shorter observed survival in the DMD-altered groups in the present study. However, previous studies often examined DMD expression, whereas the present study examined DMD alterations, which may not be directly equivalent. More recent work suggests that the prognostic role of DMD may vary between cancer types (Machado et al., 2026), indicating that its effect on tumours may be context dependent rather than universal.

LIMITATIONS AND INTERPRETATION

Limitations: DMD alterations were relatively uncommon within the analysed cohorts, occurring in approximately 5.6% to 6.6% of evaluable patients. Only 48-72 patients were present in the altered groups, with relatively few survival events. This may partly explain the wide confidence intervals around the hazard ratios.

The three datasets should not be considered completely independent of one another because their patient populations may overlap. For this reason, the hazard ratios were not averaged across the three datasets, and the similar results should be interpreted as consistency

across multiple TCGA datasets.

This study demonstrates association rather than causation. Other factors, such as age, tumour stage, and treatment, may differ between patients in the altered and unaltered groups and may influence overall survival independently of DMD status. The current study did not fully account for these factors when measuring overall survival.

Overall, the consistent direction of the Kaplan-Meier analysis, shorter median survival, and hazard-ratio estimates above 1 suggest that DMD alterations may be associated with poorer overall survival in patients with breast invasive carcinoma. However, the relatively small sample size, wide confidence intervals, overlapping TCGA datasets, and other underlying factors indicate that these results should be interpreted with caution and require analysis in larger independent datasets.

CONCLUSION

Across TCGA PanCancer Atlas, TCGA Cell 2015, and TCGA Firehose Legacy, DMD-altered patients diagnosed with breast invasive carcinoma showed poorer observed overall survival than unaltered patients. In all three datasets, DMD-altered patients showed shorter observed median overall survival, while hazard ratios consistently indicated a higher mortality hazard than in DMD-unaltered patients. However, wide confidence intervals, a small altered patient population, and other possible clinical factors limit the strength of these findings. Therefore, this analysis showed a consistent association between DMD alterations and poorer observed overall survival, while the limited altered-group size, possible overlap between patient populations, and lack of complete adjustment for clinical confounders prevent DMD alteration status from being established as an independent prognostic marker.

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