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Vitamin D Receptor rs731236 Polymorphism Modulates Cancer Cachexia Susceptibility and Overall Survival: A Real-World Study on Context-Dependent Vitamin D Signalling

Valéria Tavares
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Ana Carolina Leão Silva
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Anna Flávia Xavier
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Inês Guerra de Melo
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Tiago Ferreira
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Mariana Moreira Pires
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Cláudia Silva
Portuguese Oncology Institute of Porto (IPO Porto)

Virgínia Rocha Dias
Portuguese Oncology Institute of Porto (IPO Porto)

Maria Paula Silva
Portuguese Oncology Institute of Porto (IPO Porto)

Joana M. O. Santos
IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

Rui Medeiros
ruimedei@ipoporto.min-saude.pt

IPO Porto Research Centre (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Centre Raquel Seruca (Porto.CCC)

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Abstract

Purpose

Cancer-associated cachexia (CAC) is a complex metabolic syndrome characterised by progressive skeletal muscle loss, systemic inflammation, reduced treatment tolerance, and poor survival. Individual susceptibility to CAC varies considerably, suggesting a contribution of host genetic factors. Vitamin D plays an important role in muscle metabolism and inflammatory control through activation of the vitamin D receptor (VDR). VDR signalling influences myogenesis, mitochondrial function, insulin-like growth factor pathways, and pro-inflammatory cytokine expression, all of which are implicated in the pathophysiology of cachexia. Hence, *VDR* variants, including the rs731236 (A > G) polymorphism, which modifies receptor activity and downstream biological responses, may potentially affect CAC pathogenesis. This study aimed to investigate the association between the polymorphism and susceptibility to CAC as well as patients' overall survival (OS).

Methods

To explore the implications of the rs731236 variant, a hospital-based study was conducted with 140 adult cancer patients. CAC was assessed using Fearon criteria and the CASC-IN screening tool. Genotyping of the *VDR* rs731236 polymorphism was performed through real-time PCR. Associations with CAC and OS were analysed using chi-square tests and Kaplan-Meier survival analysis, respectively.

Results

The rs731236 GG genotype was significantly associated with a lower CAC prevalence across diagnostic approaches ($p < 0.05$). GG genotype carriers also demonstrated significantly improved OS than carriers of AA/AG genotypes (Log-rank and Tarone-Ware tests, $p < 0.05$).

Conclusion

The rs731236 polymorphism appears to influence susceptibility to CAC and cancer patient survival, adding to the existing evidence of a clinically relevant role for vitamin D signalling in supportive oncology care.

1. Introduction

Cancer-associated cachexia (CAC) is a multifactorial metabolic syndrome characterised by involuntary weight loss, progressive skeletal muscle wasting, systemic inflammation, and functional impairment (Liz-Pimenta et al., 2023). It affects up to 80% of patients with advanced malignancies, depending on the cancer type, and represents a major contributor to treatment intolerance, diminished quality of life, and

increased mortality (Alamawi et al., 2025; Mariean et al., 2023). Unlike simple starvation, CAC is driven by complex metabolic and inflammatory alterations that are not fully reversible by nutritional support alone (Peixoto da Silva et al., 2020). Despite its high prevalence and prognostic relevance, with 20% of cancer patients dying due to this condition, CAC remains underdiagnosed, undertreated, and insufficiently stratified in routine oncology practice (Alamawi et al., 2025; Mariean et al., 2023).

Chronic inflammation is a central driver of CAC pathophysiology, promoting muscle proteolysis, impaired protein synthesis, mitochondrial dysfunction, and overall altered energy metabolism. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) activate catabolic signalling pathways, disrupt anabolic responses, and contribute to endocrine resistance, ultimately accelerating muscle loss (Liz-Pimenta et al., 2023; Peixoto da Silva et al., 2020). However, substantial interindividual variability exists in the development and severity of CAC, suggesting that host-related factors, including genetic determinants, may modulate susceptibility to this syndrome (Johns et al., 2014).

Vitamin D3 (or simply vitamin D) has emerged as a central modulator of muscle function, metabolism and immune regulation, primarily via activation of the vitamin D receptor (VDR), a nuclear transcription factor expressed in skeletal muscle, immune cells, and adipose tissue. VDR signalling regulates myogenesis, muscle fibre composition, mitochondrial oxidative capacity, insulin-like growth factor 1 (IGF-1) pathways, and the production of inflammatory cytokines (Bass et al., 2020; Dzik & Kaczor, 2019; Latham et al., 2021; Saponaro et al., 2020). Vitamin D deficiency and impaired VDR signalling have been consistently associated with sarcopenia (progressive loss of skeletal muscle mass associated with ageing), frailty, and chronic inflammatory states, all of which share pathophysiological features with CAC (Bollen et al., 2022; Camperi et al., 2017; Garcia et al., 2019).

Worldwide, genetic polymorphisms are the most prevalent genetic variations among individuals, with implications for several clinical traits (Chiarella et al., 2023; de Melo et al., 2024). Genetic polymorphisms in *VDR* may influence the receptor's transcriptional activity and messenger (mRNA) stability, thereby modifying downstream biological responses to vitamin D. The rs731236 (A > G) variant, also known as TaqI, is one of the most studied *VDR* polymorphisms due to its influence on vitamin D signalling (Bollen et al., 2023; Krasniqi et al., 2021). It is a single-nucleotide polymorphism (SNP) located in the 3' untranslated region (UTR) of exon 9 of the *VDR* gene on chromosome 12q13.11 (Taşkın & Coşkun, 2025; Yates et al., 2026). It involves the substitution of adenine with guanine (or, equivalently, thymine with cytosine, depending on strand orientation) (Yates et al., 2026). Although *VDR* rs731236 does not alter the amino acid sequence of the encoded protein (i.e., synonymous variant), it may nonetheless affect gene regulation and expression through mechanisms such as altering transcription, splicing, co-translational folding, mRNA stability, and cause several other functionally-relevant alterations (Zeng & Bromberg, 2019). Given its link with altered inflammatory profiles, muscle-related phenotypes, and clinical outcomes, rs731236 has been widely studied across multiple conditions and traits, including musculoskeletal diseases (Arellano Pérez Vertti et al., 2025; Jiang et al., 2022; Şerifoğlu et al., 2024), neurological disorders (Cieślińska et al., 2017; Wang et al., 2019), infectious and immune-related diseases (Han et al., 2016; Mahto et al., 2018; Tentolouris et al., 2024; Xu & Shen, 2019), gut microbiota

composition (Gonzalez-Soltero et al., 2024), cardiometabolic conditions (Alkhedaide et al., 2021; Raljević et al., 2021) and reproductive and endocrine disorders (Donayeva et al., 2023; Feng et al., 2013; Moradkhani et al., 2024). Furthermore, the influence of *VDR* rs731236 has been evaluated across multiple malignancies with respect to disease susceptibility and prognosis (Aristizábal-Pachón et al., 2022; Guan & Wang, 2024; Liu et al., 2017; Lyu et al., 2024; Perna, Butterbach, et al., 2013; Yu et al., 2018). However, the associations are frequently inconsistent across studies, ethnic groups and disease contexts, requiring additional studies for validation. Regarding CAC, the role of *VDR* rs731236 remains poorly explored, with most previous studies focusing on either vitamin D levels or single tumour types, rather than the intersection of host genetics, muscle wasting, and patient survival. Given existing knowledge gaps, this study aimed to investigate the association between this polymorphism and susceptibility to CAC and cancer patient survival.

2. Methods

2.1. Study design and participants

A retrospective cohort study was conducted, enrolling cancer patients admitted at the Portuguese Institute of Oncology of Porto (IPO Porto) for either first-line treatment or palliative care. The cohort included individuals of European descent aged 19 years or older, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of ≤ 3. Exclusion criteria comprised patients who requested a second medical opinion, were receiving medication for anorexia, had cognitive deficits, faced language barriers or refused to participate in the study. Based on these criteria, a total of 140 cancer patients were recruited between March 2023 and May 2024, with a mean follow-up of 76.3 ± 4.0 weeks. All participants provided informed consent.

At enrolment, patients' CAC-related data were collected using Fearon's criteria and the CASC-IN questionnaires. Anthropometric measurements were also taken, including weight on a digital iHealth Nexus HS2S® scale and height on a stadiometer. To evaluate the participants' nutritional health and inflammatory profiles, the study employed the neutrophil-to-lymphocyte ratio (NLR) and the prognostic nutritional index (PNI). The PNI is quantified by adding the serum albumin level (g/L) to five times the absolute lymphocyte count [serum albumin value (g/L) + 5X total lymphocytes (10^9/L)]. For NLR, it is calculated as the absolute neutrophil count divided by the absolute lymphocyte count (Silva et al., 2024). These ratios are relevant in the study of CAC, as systemic inflammation is the fundamental mechanism driving that condition (Zhang et al., 2021).

At the time of recruitment, blood samples were also collected, and clinical history and demographic information were retrieved from patients' medical records. Women comprised 54.3% (N = 76) of the study population. At enrolment, the mean age was 63.18 ± 1.1 years, with 47.1% (N = 66) of patients being over 63 years old. A body mass index (BMI) < 26 kg/m² was observed in 52.1% (N = 73) of participants. Concerning performance status, 48.3% (N = 57) of patients had an ECOG-PS of 0, 33.1% (N = 39) had a score of 1, 16.1% (N = 19) had a score of 2, and 2.5% (N = 3) had a score of 3. Metastatic

disease was present in 64.3% (N = 90) of the cohort, while 5.7% (N = 8) reported a history of other malignancies. Details regarding tumour types and treatment modalities are presented in Fig. 1.

This study was approved by the Human Research Ethics Committee of IPO Porto (CES. 131/022, approved on 28th July 2022).

2.2. Sample processing and genomic DNA extraction

At enrolment, peripheral blood was obtained from participants through standard venous blood collection. The specimens were placed in EDTA-anticoagulated tubes to prevent coagulation.

Extraction of genomic DNA was performed using the MagaBio Plus Virus DNA/RNA Purification Kit II (BSC71S1E, Bioflux®, Japan) in combination with the MGISP-NE32 automated nucleic acid extraction system (MGI Tech), strictly adhering to the supplier's protocol. The yield and purity of the isolated DNA were evaluated spectrophotometrically using a NanoDrop Lite instrument (Thermo Fisher Scientific, Waltham, MA, USA). Verified DNA samples were subsequently stored at − 20°C until further analysis.

2.3. SNP genotyping

Genotypic analysis of the *VDR* rs731236 polymorphism was carried out using a StepOnePlus real-time PCR platform (Applied Biosystems, Carlsbad, CA, USA) employing a fluorescence-based TaqMan allelic discrimination approach. The preparation of the amplification reactions was previously described (Marques et al., 2024; Silva et al., 2022; Tavares et al., 2023). Briefly, the total volume for each reaction was 6 µL, comprising 2.5 µL of TaqPath™ ProAmp™ Master Mix at working concentration, 0.125 µL of the specific TaqMan® SNP Genotyping Assay (C___2404008_10 targeting the *VDR* rs731236 variant; **Supplementary Table S1**), 1 µL of template DNA, and nuclease-free water to reach the final reaction volume. Thermal cycling parameters followed a previously established protocol (Tavares et al., 2023).

To monitor potential contamination, two no-template controls (i.e., negative controls) were incorporated into each run. In addition, the reproducibility of genotyping was validated by repeating the analysis in 20% of randomly selected samples. Interpretation of genotype calls was performed independently by three investigators who were unaware of the corresponding clinical and pathological information.

2.4. Statistical analysis

Quantitative analyses and Fig. generation were carried out using IBM SPSS Statistics for Windows, version 30.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Genotype frequencies observed in the study cohort were contrasted with reference data from the Iberian population available through the Ensembl database (https://www.ensembl.org/index.html, last accessed on the 28th of December of 2025). Conformity between observed and expected genotype distributions was examined by testing for Hardy-Weinberg equilibrium (HWE) using the Chi-square (χ^2) test of independence.

The distributional properties of continuous variables were assessed using the Kolmogorov-Smirnov test. Depending on whether the variables followed a parametric or non-parametric distribution, data were categorised based on either mean or median values, respectively. Regarding PNI and NLR, initially, patients were ranked according to each marker and divided into tertiles. These three-tier classifications were subsequently combined into binary categories. For PNI, the lowest tertile (≤ 44.2) was designated as the low group, whereas the remaining two tertiles constituted the high group. In contrast, NLR values were considered low when falling within the first two tertiles (< 3.6) and high when belonging to the upper tertile (≥ 3.6).

Cachexia status was assessed using the Fearon criteria, the CASC-IN classification system, and a combined approach. In the latter, patients were assigned to a group only if the Fearon and CASC-IN systems yielded the same classification. For these three diagnostic strategies, cachexia status was evaluated in two ways: firstly, using three categories (non-cachectic, pre-cachectic and cachectic); and secondly, via a binary classification where pre-cachectic and cachectic patients were grouped as cachexia-positive.

Relationships between the *VDR* rs731236 variant and CAC occurrence, as well as demographic and clinicopathological parameters, were evaluated using the χ^2 test or Fisher's exact test, as appropriate based on expected cell frequencies. Logistic regression analyses were conducted to estimate the CAC risk [odds ratio (OR) and 95% confidence intervals (95% CI)] associated with each SNP genotype.

The clinical outcome evaluated in this study was overall survival (OS), which was defined as the time elapsed from study inclusion (corresponding to cachexia assessment) to death from any cause or to the most recent follow-up for censored cases. Survival outcomes related to *VDR* genetic variation were explored using Kaplan-Meier methodology. Group comparisons were performed with either the log-rank test or the Tarone-Ware test, selected according to compliance with proportional hazard assumptions and the genetic inheritance model best supported by preliminary survival curve inspection. The impact of the SNP on the risk of patient death was also examined via Cox regression analysis. Multivariable Cox analysis was conducted, adjusting for relevant demographic and clinicopathological parameters. Due to cohort size, subgroup analyses according to tumour type and cancer treatment approaches were not conducted. To evaluate data stability and reliability, bootstrap resampling (1,000 iterations) was carried out.

All hypothesis testing was conducted using two-tailed procedures, and statistical significance was established at a threshold of $p < 0.05$.

3. Results

3.1. Distribution of *VDR* rs731236 genotypes

Genotype distributions for *VDR* rs731236 in the study population and the reference Iberian population described in the Ensembl database (https://www.ensembl.org/index.html, last accessed on the 28th of

December of 2025) are indicated in Fig. 2. Compared with the reference population, the distribution of SNP genotypes did not differ significantly (χ^2 test, $p = 0.551$), indicating that the variant is consistent with HWE expectations.

Notably, SNP genotype distributions did not differ significantly by patient demographic or clinicopathological variables (χ^2 test or Fisher's exact test, $p > 0.05$).

3.2. Association between *VDR* rs731236 and CAC status

Cachexia prevalence in the study cohort was approximately 30% using Fearon criteria, CASC-IN, or both combined tools in the diagnosis (Fig. 3).

A significant association was observed between *VDR* rs731236 genotypes and CAC status (χ^2 test or Fisher's exact test, $p < 0.05$). Across all diagnostic criteria, the SNP GG genotype was consistently more prevalent among individuals without CAC (Table 1).

Table 1

Distribution of *VDR* rs731236 genotypes across groups (no cachexia, pre-cachexia, and cachexia) as defined by FEARON criteria, CASC-IN, and combined assessment tools.

Diagnostic approach		*VDR* rs731236 genotypes						
		GG N (%)	AG N (%)	AA N (%)	GG N (%)	AG + AA N (%)	GG + AG N (%)	AA N (%)
Fearon criteria	**No CAC**	22 (81.5)	34 (58.6)	27 (49.1)	22 (81.5)	61 (54.0)	56 (65.9)	27 (49.1)
	Pre-CAC	3 (11.1)	7 (12.1)	5 (9.1)	3 (11.1)	12 (10.6)	10 (11.8)	5 (9.1)
	CAC	2 (7.4)	17 (29.3)	23 (41.8)	2 (7.4)	40 (35.4)	19 (22.4)	23 (41.8)
	p-Value	**0.030**			**0.012**		**0.048**	
CASC-IN	**No CAC**	22 (81.5)	37 (63.8)	27 (50.9)	22 (81.5)	64 (57.7)	59 (69.4)	27 (50.9)
	Pre-CAC	3 (11.1)	4 (6.9)	5 (9.4)	3 (11.1)	9 (8.1)	7 (8.2)	5 (9.4)
	CAC	2 (7.4)	17 (29.3)	21 (39.6)	2 (7.4)	38 (34.2)	19 (22.4)	21 (39.6)
	p-Value	**0.027**			**0.028**		0.075	
Combined tools	**No CAC**	20 (87.0)	33 (62.3)	24 (51.1)	20 (87.0)	57 (57.0)	53 (69.7)	24 (51.1)
	Pre-CAC	1 (4.3)	3 (5.7)	2 (4.3)	1 (4.3)	5 (5.0)	4 (5.3)	2 (4.3)
	CAC	2 (8.7)	17 (32.1)	21 (44.7)	2 (8.7)	38 (38.0)	19 (25.0)	21 (44.7)
	p-Value	**0.026**			**0.011**		0.081	

Bold values were deemed statistically significant. Abbreviations: CAC, cancer-associated cachexia; N, number of patients.

Consistently, when pre-CAC and CAC patients were combined into a single entity group, the significant association between *VDR* rs731236 genotypes and CAC status remained (Table 2). Under the recessive genetic model (GG vs. AG/AA), for which significant results were observed, the GG genotype was associated with a significantly lower disease risk according to the Fearon criteria [OR = 0.27; 95% CI, 0.09–0.75], the CASC-IN criteria (OR = 0.32; 95% CI, 0.11–0.90), and the combined assessment tool (OR = 0.20; 95% CI, 0.06–0.71).

Table 2
Distribution of *VDR* rs731236 genotypes by disease status (no cachexia vs. pre-cachexia/cachexia) according to FEARON criteria, CASC-IN, and combined assessment tools.

Diagnostic approach		*VDR* rs731236 genotypes						
		GG N (%)	AG N (%)	AA N (%)	GG N (%)	AG + AA N (%)	GG + AG N (%)	AA N (%)
Fearon criteria	**No CAC**	22 (81.5)	34 (58.6)	27 (49.1)	22 (81.5)	61 (54.0)	56 (65.9)	27 (49.1)
	CAC/ Pre-CAC	5 (18.5)	24 (41.4)	28 (50.9)	5 (18.5)	52 (46.0)	29 (34.1)	28 (50.9)
	p-Value	**0.019**			**0.017**		0.072	
CASC-IN	**No CAC**	22 (81.5)	37 (63.8)	29 (52.7)	22 (81.5)	66 (58.4)	59 (69.4)	29 (52.7)
	CAC/ Pre-CAC	5 (18.5)	21 (36.2)	26 (47.3)	5 (18.5)	47 (41.6)	26 (30.6)	26 (47.3)
	p-Value	**0.040**			**0.045**		0.069	
Combined tools	**No CAC**	20 (87.0)	33 (62.3)	24 (51.1)	20 (87.0)	57 (57.0)	53 (69.7)	24 (51.1)
	CAC/ Pre-CAC	3 (13.0)	20 (37.7)	23 (48.9)	3 (13.0)	43 (43.0)	23 (30.3)	23 (48.9)
	p-Value	**0.014**			**0.015**		0.059	

Bold values were deemed statistically significant. Abbreviations: CAC, cancer-associated cachexia; N, number of patients.

3.3. Association between *VDR* rs731236 and patient survival

In the overall cohort (N = 140), carriers of the SNP GG genotype exhibited a significantly longer OS than patients with AA/AG genotypes (Fig. 4). Individuals harbouring the GG genotype experienced a 76% reduction in the risk of death compared with their counterparts [hazard ratio (HR) = 0.24; 95% CI, 0.07–0.76; $p = 0.016$]. Notably, this association remained robust after adjustment for potential confounding variables, confirming the independent prognostic value of the *VDR* rs731236 GG genotype (Table 3).

To specifically assess the impact of *VDR* rs731236 on survival in CAC patients, a subgroup analysis was performed. In this CAC-only population, no significant association between SNP genotypes and survival was detected, irrespective of the diagnostic criteria or genetic model applied (Log-rank and Tarone-Ware tests, $p > 0.05$).

Table 3
Multivariable Cox analysis on the risk of death.

Variable	aHR	95%CI	*p*-Value	*Bootstrap p-Value*
VDR rs731236 (GG vs. AA/AG *)	0.23	**0.07–0.75**	**0.015**	**0.006**
Patient sex (female vs. male *)	1.00	0.53–1.90	0.992	0.990
Patient age at recruitment (≥ 63 vs. < 63 years *)	1.67	0.88–3.115	0.120	0.141
BMI at recruitment (< 26 vs. ≥ 26 kg/m^2 *)	1.41	0.76–2.61	0.273	0.276
PNI (≤ 44.2 vs. > 44.2 *)	2.01	**1.03–3.92**	**0.040**	0.058
NLR (≥ 3.6 vs. < 3.6 *)	3.56	**1.79–7.06**	**< 0.001**	**0.002**

Bold values were deemed statistically significant. * - reference group. Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

4. Discussion

Muscle regeneration is a multifaceted process that requires the recovery of mitochondrial activity and the activation of satellite cells, the intrinsic stem cells responsible for skeletal muscle repair. In recent years, growing evidence has implicated vitamin D signalling as an important regulator of skeletal muscle metabolism, regeneration, and protein turnover, pathways that are critically disrupted in CAC and that influence patient outcomes (Latham et al., 2021). In this context, the present study investigated the association between the *VDR* rs731236 polymorphism and clinical outcomes in cancer patients, focusing on CAC susceptibility and overall survival. Our findings indicate that GG genotype carriers have a lower risk of developing cachexia and demonstrated improved overall survival, independent of CAC status, compared with individuals carrying the AA or AG genotypes. To understand how the GG genotype may confer protection against CAC, it is necessary to consider the role of vitamin D in skeletal muscle.

Vitamin D is a pleiotropic hormone primarily produced in the skin through ultraviolet-dependent synthesis. It is subsequently converted in the liver into 25-hydroxyvitamin D, the primary circulating form, and then further hydroxylated to its active form, $1,25(OH)_2D_3$. Although this final activation step primarily occurs in the kidney, several other tissues also possess the enzymatic machinery required for local vitamin D activation (Camperi et al., 2017). In the circulation, $1,25(OH)_2D_3$ is transported to target tissues by vitamin D-binding proteins. Its biological effects are mainly mediated by its receptor, VDR, a widely expressed nuclear receptor (Rosen et al., 2012). Upon ligand binding, the VDR heterodimerises with the retinoid X receptor and regulates gene transcription via interactions with vitamin D response elements (VDREs) within promoters of target genes involved in calcium and bone metabolism, cell growth and differentiation, immune response and function (Carlberg, 2022; Voltan et al., 2023). In addition to these classic genomic actions, vitamin D also exerts rapid non-genomic effects via key signalling cascades,

including the mitogen-activated protein kinase (MAPK) cascade, the phosphoinositide 3-kinase/protein kinase B (PI3K-Akt) pathway, and the mechanistic target of rapamycin (mTOR) signalling axis, which intersect with metabolic and anabolic networks governing muscle mass and function, namely modulation of mitochondrial function and intracellular calcium handling (Bollen & Atherton, 2021; Latham et al., 2021; Zhao & Simpson, 2010).

Within skeletal muscle, VDR expression is dynamic and stage-specific, being most abundant in proliferating myoblasts and regenerating fibres and minimal in mature myofibres. This distribution suggests that vitamin D primarily regulates muscle regeneration and satellite cell activity rather than the contractile function of fully differentiated muscle (Braga et al., 2017; Girgis et al., 2014; Sandgren et al., 1991; Wang & DeLuca, 2011). Consistently, $1,25(OH)_2D_3$ modulates myogenesis by limiting early myoblast proliferation through cell-cycle arrest, while promoting later differentiation and myotube formation under specific conditions. At the molecular level, vitamin D influences the expression of key regulators of muscle mass, including Forkhead box O (FOXO) transcription factors, IGF-1 signalling components, myostatin, and integrins, thereby coordinating protein synthesis, degradation and repair processes (Bollen & Atherton, 2021; Li et al., 2021; Polly & Tan, 2014). The transcriptional activity of these pathways is further modulated by multiple coactivators and corepressors, enabling tissue- and context-specific regulation of gene expression (Camperi et al., 2017; Rosen et al., 2012).

Under physiological conditions, vitamin D is well recognised for its anti-inflammatory and anabolic effects, including suppression of pro-inflammatory cytokines, inhibition of the ubiquitin-proteasome pathway, which drives muscle protein breakdown, while promoting muscle regeneration via protein synthesis (Garcia et al., 2011; Latham et al., 2021; Salles et al., 2013). Salles et al. (2013) demonstrated that vitamin D enhances muscle cell responsiveness to insulin and leucine (Salles et al., 2013). Similarly, Garcia et al. (2011) showed that vitamin D promotes muscle cell maturation, supporting muscle regeneration (Garcia et al., 2011). These studies indicate that vitamin D supports muscle homeostasis, and its deficiency may predispose to muscle atrophy.

Intriguingly, the relationship between vitamin D signalling and muscle homeostasis appears to be more complex in the setting of CAC, which is characterised by chronic systemic inflammation, metabolic dysregulation, and impaired regenerative capacity (Liz-Pimenta et al., 2023; Peixoto da Silva et al., 2020). Pro-inflammatory cytokines elevated in CAC, including TNF-α and IL-6, directly promote proteolysis while suppressing anabolic signalling, thereby accelerating muscle loss. Within this inflammatory environment, dysregulation of VDR may paradoxically exacerbate muscle wasting rather than preserve muscle mass. Camperi et al. (2017) provided critical evidence of this molecular paradox using tumour-bearing animal models and human muscle biopsies (Camperi et al., 2017). They found that while circulating vitamin D levels decrease significantly in CAC, *VDR* expression in skeletal muscle simultaneously increases. Although this rise was initially interpreted as a compensatory response to low serum vitamin D levels, supplementation failed to reverse the muscle loss and instead further elevated *VDR* expression, suggesting a maladaptive feedback loop. The authors proposed that under the inflammatory conditions of CAC, vitamin D signalling is reprogrammed to act as a molecular brake on myogenic differentiation by

suppressing myogenin, a key regulator of muscle fibre formation, effectively stalling regeneration. Consequently, vitamin D supplementation in this context may be counterproductive, as it can exacerbate *VDR* overexpression without restoring muscle repair (Camperi et al., 2017; Yang et al., 2020). Collectively, these findings suggest that the biological effects of vitamin D are highly context-dependent and that dysregulated VDR activity, rather than vitamin D deficiency alone, may drive muscle pathology in CAC. Such complexity challenges the conventional view that vitamin D supplementation is universally beneficial in cancer patients, particularly those with active muscle wasting (Camperi et al., 2017).

Genetic polymorphisms in *VDR* may further modify individual responses to vitamin D signalling. The rs731236 polymorphism has been associated with altered receptor transcriptional activity or stability, although its functional consequences appear to be context-dependent. Tomei et al. (2020) conducted an interventional study in a healthy cohort composed mainly of women of Arab ancestry to assess the association between response to vitamin D supplementation and genetic variants in vitamin D-related genes. They found that the rs731236 GG genotype was significantly associated with a "vitamin D sufficiency" state [serum 25(OH)D levels ≥ 30 ng/mL], and those with this genotype had a higher response to vitamin D supplementation (Tomei et al., 2020).

Several studies have explored associations between rs731236 and musculoskeletal traits. The polymorphism has been associated with hand grip strength in schoolchildren (Bozsodi et al., 2016). However, other investigations did not detect significant associations with muscle strength or sarcopenic traits, suggesting that other *VDR* variants, such as rs1544410 (BsmI) and rs7975232 (ApaI), may contribute more strongly to these phenotypes (Bahat et al., 2010; Krasniqi et al., 2021; Walsh et al., 2016; Wang et al., 2006). Notably, rs731236 frequently occurs in linkage disequilibrium with these polymorphisms, indicating that haplotypic effects may amplify its functional consequences (Krasniqi et al., 2021). Among Chinese Han adults, the rs731236 variant was associated with differential adaptations to resistance training, with sex-specific effects. Namely, in women, AA genotype carriers achieved greater strength and power gains, whereas AG genotype carriers demonstrated more pronounced improvements in body composition (Yang & Li, 2026). Ovesjö et al. (2016) reported that carriers of the CC genotype (or GG genotype, depending on the DNA strand) had a fourfold increased risk of developing myopathy compared to individuals with the TT genotype (or AA genotype) (Ovesjö et al., 2016). However, a follow-up study by the same research group, using *in vitro* experiments on primary human myoblasts, suggested that the polymorphism does not directly influence the inhibitory effects of vitamin D on myoblast proliferation or differentiation. However, it has been shown that the CC genotype (or GG genotype) correlates with a higher number of VDREs, which can lead to exaggeration of vitamin D response, suppressing genes related to myogenic fusion, thus preventing the repair of damaged muscle fibres (Saini et al., 2019). In the present study, the GG genotype (previously associated with vitamin D sufficiency) was linked to a protective effect against CAC development. This finding appears to contrast the cumulative evidence in musculoskeletal diseases but can be reconciled through the “molecular paradox” of vitamin D signalling in the context of CAC, whereby inflammatory and metabolic dysregulation reprograms VDR activity, altering its effects on muscle homeostasis (Camperi et al., 2017).

In addition to CAC susceptibility, *VDR* rs731236 was also associated with cancer patient survival in the overall cohort (regardless of CAC status), independent of clinical covariates such as patient sex, age, BMI, and inflammatory indices (PNI and NLR). This observation suggests that the polymorphism may influence prognosis through mechanisms extending beyond muscle wasting alone. Indeed, VDR signalling exerts pleiotropic systemic effects, interacting with multiple metabolic and immune pathways, including the regulation of inflammatory cytokine profiles, oxidative stress responses, mitochondrial function, insulin sensitivity and autophagy, all of which have been independently linked to cancer progression, treatment tolerance and survival (Latham et al., 2021). Consequently, genetic variation in *VDR* may affect clinical outcomes through broad host-level mechanisms, irrespective of cachexia status. By contrast, no significant associations were observed in analyses stratified by CAC status, most likely reflecting the smaller subgroup sizes and limited statistical power rather than a true absence of effect. These findings should also be interpreted within the broader context of vitamin D biology.

Vitamin D deficiency is highly prevalent across diverse geographic regions, particularly among older adults, and has been associated with reduced physical performance and increased mortality risk (Bollen et al., 2022; Wong et al., 2013). This deficiency is even more common in patients with advanced cancer and correlates strongly with greater pain burden, fatigue, and increased opioid requirements (Habib et al., 2020; Martínez-Alonso et al., 2016; Wu et al., 2025). Although most investigations of rs731236 have focused on cancer susceptibility, accumulating evidence suggests that this polymorphism may also influence prognosis, albeit with inconsistent findings across tumour types. In a breast cancer cohort, carriers of the GG genotype exhibited significantly higher cancer-specific mortality (Perna, Butterbach, et al., 2013). Similarly, in non-resectable lung cancer, rs731236 was an independent predictor of progression-free survival and OS, with GG carriers again showing poorer outcomes (Pineda Lancheros et al., 2021). Conversely, in metastatic colorectal cancer, GG genotype carriers demonstrated significantly improved OS compared with A allele carriers [70]. In line with this heterogeneity, a large pooled colorectal cancer analysis reported no significant association between rs731236 and either cancer-specific or all-cause mortality (Perna, Hoffmeister, et al., 2013), and a study in head and neck squamous cell carcinoma likewise found no statistically significant survival effects (Hama et al., 2011). These heterogeneous results, including those from the present study, suggest that the prognostic impact of rs731236 is tumour- and context-dependent, likely influenced by factors such as inflammatory burden, tumour microenvironment, patient comorbidities, and CAC prevalence. Notably, in this study cohort, which encompassed patients with diverse tumour types, stratified analyses were not feasible due to small subgroup sizes, limiting statistical power and the ability to detect tumour-specific effects.

Overall, this study provides a personalised medicine perspective, emphasising the importance of host genetic factors when evaluating supportive or nutritional interventions in patients with cancer. Despite the promising findings, this study had some limitations that should be noted. The single-centre design and modest sample size may have limited statistical power and generalisability, and the absence of circulating vitamin D measurements precluded direct assessment of genotype-phenotype relationships. Nevertheless, the study had important strengths, including the application of two cachexia classification systems and robust genotyping methodology, which enhance the reliability of the observations. Future

research incorporating larger, multicentre cohorts, biochemical profiling of vitamin D status, evaluation of muscle proteolytic markers and/or longitudinal muscle imaging, functional assessments, and mechanistic analyses is warranted. Such studies will be critical to clarify the mechanistic and clinical implications of *VDR* variants and to explore the potential of genotype-guided therapeutic strategies. Additionally, investigating other *VDR* polymorphisms may further expand understanding of how inherited variation influences muscle homeostasis and cancer outcomes. Finally, future studies should address potential sex-specific effects of rs731236 on CAC development and cancer survival, which could not be assessed in the present study due to an unbalanced sex distribution and limited statistical power in subgroup analyses.

5. Conclusion

CAC represents one of the most severe and clinically challenging complications in cancer patients. Thus, it is important to identify biological determinants that influence both its susceptibility and prognosis. Hence, this real-world study examined the implications of *VDR* rs731236 in a cohort of cancer patients. Our findings demonstrate that this polymorphism is significantly associated with both outcomes. Although routine genetic screening is not yet standard practice in oncology supportive care, these findings add to the growing body of evidence emphasising the importance of host genetic factors in shaping clinical outcomes. Future studies integrating *VDR* rs731236 with assessments of circulating vitamin D status and targeted supportive interventions are warranted to clarify the translational relevance of these associations. Moreover, further research is needed to determine the clinical effectiveness of vitamin D supplementation in preventing or mitigating active CAC. Importantly, the broader literature indicates that the biological and clinical effects of *VDR* rs731236 and vitamin D signalling are context-dependent. While vitamin D is widely recognised for its pro-regenerative actions in skeletal muscle under physiological conditions, these benefits may not translate directly to pathological states such as CAC. Likewise, the prognostic significance of rs731236 remains inconsistent across malignancies. Overall, these findings reinforce the concept that vitamin D signalling in cancer is highly context-dependent and that genetic determinants of *VDR* may represent clinically relevant modifiers of cancer patient outcomes.

Declarations

Competing Interests:

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Compliance with Ethical Standards:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Human Research Ethics Committee of IPO Porto (code 131/022, approved on 28th July 2022).

Consent to Participate:

Informed consent was obtained from all individual participants included in the study.

Clinical Trial Number

Not applicable.

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Author Contribution

Author contributions: Conceptualisation, V.T. and A.F.X.; formal analysis, V.T. and R.M.; Methodology, V.T., A.C.L., I.G.d.M., T.F., M.M.P. and J.M.O.S.; investigation, V.T., A.C.L., I.G.d.M., T.F., M.M.P, V.R.D., C.S., M.P.S.; and J.M.O.S.; resources, R.M.; writing-original draft preparation, V.T.; writing-review and editing, V.T., A.F.X., I.G.d.M., T.F., M.M.P, A.C.L., V.R.D., C.S., M.P.S., R.M and J. M.O.S.; supervision, R.M and J. M.O.S.; funding acquisition, V.T., I.G.d.M., T.F. J.M.O.S and R.M. All authors have read and agreed to the published version of the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Data Availability

Data Availability: The data presented in this study are available from the corresponding author upon request.

References

1. Alamawi N, Alsharawneh A, Abualruz H, AbuRuz SM (2025) Cancer Cachexia in Clinical Practice: A Review of Treatment Barriers Among Cancer Patients. Eur J Cancer Care 2025(1):6659047
2. Alkhedaide A, Mergani A, Aldhahrani A, Sabry A, Soliman M, Nassan M, Ismail T (2021) Association of vitamin D receptor gene polymorphisms with type 2 diabetes mellitus in Taif population: a case-control study. Brazilian J Biology 84:e250739
3. Arellano Pérez Vertti RD, Ramírez A, González DO, Galarza FF, Hinojosa P, Méndez Hernández AI, Muñoz A, Flores MV, Ramírez A, Argüello DF, Beltrán CS, Argüello Astorga R (2025) Association of vitamin D blood deficiency and the rs731236 polymorphism vitamin D receptor with primary knee osteoarthritis in subjects from Mexico. Clin Rheumatol 44(3):1329–1335
4. Aristizábal-Pachón AF, González-Giraldo Y, Garcia AY, Suarez DX, Rodríguez A, Gonzalez-Santos J (2022) Association between VDR gene polymorphisms and melanoma susceptibility in a colombian population. Asian Pac J Cancer Prevention: APJCP 23(1):79
5. Bahat G, Saka B, Erten N, Ozbek U, Coskunpinar E, Yildiz S, Sahinkaya T, Karan A, M (2010) BsmI polymorphism in the vitamin D receptor gene is associated with leg extensor muscle strength in elderly men. Aging Clin Exp Res 22(3):198–205
6. Bass JJ, Nakhuda A, Deane CS, Brook MS, Wilkinson DJ, Phillips BE, Philp A, Tarum J, Kadi F, Andersen D (2020) Overexpression of the vitamin D receptor (VDR) induces skeletal muscle hypertrophy. Mol metabolism 42:101059
7. Bollen SE, Atherton PJ (2021) Myogenic, genomic and non-genomic influences of the vitamin D axis in skeletal muscle. Cell Biochem Funct 39(1):48–59
8. Bollen SE, Bass JJ, Fujita S, Wilkinson D, Hewison M, Atherton PJ (2022) The Vitamin D/Vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia. Cell Signal 96:110355
9. Bollen SE, Bass JJ, Wilkinson DJ, Hewison M, Atherton PJ (2023) The impact of genetic variation within the vitamin D pathway upon skeletal muscle function: a systematic review. J Steroid Biochem Mol Biol 229:106266
10. Bozsodi A, Boja S, Szilagyi A, Somhegyi A, Varga PP, Lazary A (2016) Muscle strength is associated with vitamin D receptor gene variants. J Orthop Res 34(11):2031–2037
11. Braga M, Simmons Z, Norris KC, Ferrini MG, Artaza JN (2017) Vitamin D induces myogenic differentiation in skeletal muscle derived stem cells. Endocr Connections 6(3):139–150
12. Camperi A, Pin F, Costamagna D, Penna F, Menduina ML, Aversa Z, Zimmers T, Verzaro R, Fittipaldi R, Caretti G (2017) Vitamin D and VDR in cancer cachexia and muscle regeneration. Oncotarget 8(13):21778
13. Carlberg C (2022) Vitamin D and its target genes. Nutrients 14(7):1354

14. Chiarella P, Capone P, Sisto R (2023) Contribution of genetic polymorphisms in human health. Int J Environ Res Public Health 20(2):912
15. Cieślińska A, Kostyra E, Chwała B, Moszyńska-Dumara M, Fiedorowicz E, Teodorowicz M, Savelkoul HF (2017) Vitamin D receptor gene polymorphisms associated with childhood autism. Brain Sci 7(9):115
16. de Melo IG, Tavares V, Pereira D, Medeiros R (2024) Contribution of endothelial dysfunction to Cancer susceptibility and progression: a comprehensive narrative review on the genetic risk component. Curr Issues Mol Biol 46(5):4845–4873
17. Donayeva A, Amanzholkyzy A, Nurgaliyeva R, Gubasheva G, Saparbayev S, Ayaganov D, Kaldybayeva A, Abdelazim IA, Farghali MM (2023) Vitamin D and vitamin D receptor polymorphism in Asian adolescents with primary dysmenorrhea. BMC Womens Health 23(1):414
18. Dzik KP, Kaczor JJ (2019) Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol 119(4):825–839
19. Feng M, Li H, Chen S-F, Li W-F, Zhang F-B (2013) Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. Endocrine 43(2):318–326
20. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN (2011) 1, 25 (OH) 2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. Endocrinology 152(8):2976–2986
21. Garcia M, Seelaender M, Sotiropoulos A, Coletti D, Lancha AH Jr (2019) Vitamin D, muscle recovery, sarcopenia, cachexia, and muscle atrophy. Nutrition 60:66–69
22. Girgis CM, Clifton-Bligh RJ, Mokbel N, Cheng K, Gunton JE (2014) Vitamin D signaling regulates proliferation, differentiation, and myotube size in C2C12 skeletal muscle cells. Endocrinology 155(2):347–357
23. Gonzalez-Soltero R, Tabone M, Larrosa M, Bailen M, Bressa C (2024) VDR gene TaqI (rs731236) polymorphism affects gut microbiota diversity and composition in a Caucasian population. Front Nutr 11:1423472
24. Guan M, Wang Y (2024) Common variants of vitamin D receptor gene polymorphisms and risk of gastric cancer: A meta-analysis. Medicine 103(35):e39527
25. Habib AM, Nagi K, Thillaiappan NB, Sukumaran V, Akhtar S (2020) Vitamin D and its potential interplay with pain signaling pathways. Front Immunol 11:820
26. Hama T, Norizoe C, Suga H, Mimura T, Kato T, Moriyama H, Urashima M (2011) Prognostic significance of vitamin D receptor polymorphisms in head and neck squamous cell carcinoma. PLoS ONE, 6(12), e29634
27. Han J-C, Du J, Zhang Y-J, Qi G-B, Li H-B, Zhang YJ, Yu X-l (2016) Vitamin D receptor polymorphisms may contribute to asthma risk. J Asthma 53(8):790–800
28. Jiang LL, Zhang C, Zhang Y, Ma F, Guan Y (2022) Associations between polymorphisms in VDR gene and the risk of osteoporosis: a meta-analysis. Arch Physiol Biochem 128(6):1637–1644

29. Johns N, Tan B, MacMillan M, Solheim T, Ross J, Baracos V, Damaraju S, Fearon K (2014) Genetic basis of interindividual susceptibility to cancer cachexia: selection of potential candidate gene polymorphisms for association studies. J Genet 93:893–916
30. Krasniqi E, Boshnjaku A, Wagner K-H, Wessner B (2021) Association between polymorphisms in vitamin D pathway-related genes, vitamin D status, muscle mass and function: a systematic review. Nutrients 13(9):3109
31. Latham CM, Brightwell CR, Keeble AR, Munson BD, Thomas NT, Zagzoog AM, Fry CS, Fry JL (2021) Vitamin D promotes skeletal muscle regeneration and mitochondrial health. Front Physiol 12:660498
32. Li A, Shen P, Liu S, Wang J, Zeng J, Du C (2021) Vitamin D alleviates skeletal muscle loss and insulin resistance by inducing vitamin D receptor expression and regulating the AMPK/SIRT1 signaling pathway in mice. Food Sci Technol 42:e47921
33. Liu S, Cai H, Cheng W, Zhang H, Pan Z, Wang D (2017) Association of VDR polymorphisms (Taq I and Bsm I) with prostate cancer: a new meta-analysis. J Int Med Res 45(1):3–10
34. Liz-Pimenta J, Tavares V, Neto BV, Santos JM, Guedes CB, Araújo A, Khorana AA, Medeiros R (2023) Thrombosis and cachexia in cancer: Two partners in crime? Crit Rev Oncol/Hematol 186:103989
35. Lyu C, Yin X, Li Z, Wang T, Xu R (2024) Vitamin D receptor gene polymorphisms and multiple myeloma: A meta-analysis. Clin Experimental Med 24(1):118
36. Mahto H, Tripathy R, Das BK, Panda AK (2018) Association between vitamin D receptor polymorphisms and systemic lupus erythematosus in an Indian cohort. Int J Rheum Dis 21(2):468–476
37. Mariean CR, Tiucă OM, Mariean A, Cotoi OS (2023) Cancer cachexia: new insights and future directions. Cancers 15(23):5590
38. Marques IS, Tavares V, Vieira Neto B, Lopes LR, Goes RA, Guimarães JAM, Perini JA, Medeiros R (2024) Genetic variations in susceptibility to traumatic muscle injuries and muscle pain among Brazilian high-performance athletes. Int J Mol Sci 25(6):3300
39. Martínez-Alonso M, Dusso A, Ariza G, Nabal M (2016) Vitamin D deficiency and its association with fatigue and quality of life in advanced cancer patients under palliative care: a cross-sectional study. Palliat Med 30(1):89–96
40. Moradkhani A, Azami M, Assadi S, Ghaderi M, Azarnezhad A, Moradi Y (2024) Association of vitamin D receptor genetic polymorphisms with the risk of infertility: a systematic review and meta-analysis. BMC Pregnancy Childbirth 24(1):398
41. Ovesjö ML, Skilving I, Bergman P, Rane A, Ekström L, Björkhem-Bergman L (2016) Low Vitamin D Levels and Genetic Polymorphism in the Vitamin D Receptor are Associated with Increased Risk of Statin-Induced Myopathy. Basic Clin Pharmacol Toxicol 118(3):214–218
42. Peixoto da Silva S, Santos JM, Costa e Silva MP, Gil da Costa RM, Medeiros R (2020) Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. J Cachexia Sarcopenia Muscle 11(3):619–635

43. Perna L, Butterbach K, Haug U, Schöttker B, Müller H, Arndt V, Holleczek B, Burwinkel B, Brenner H (2013) Vitamin D receptor genotype rs731236 (Taq1) and breast cancer prognosis. Cancer Epidemiol Biomarkers Prev 22(3):437–442
44. Perna L, Hoffmeister M, Schöttker B, Arndt V, Haug U, Holleczek B, Burwinkel B, Ordóñez-Mena JM, Brenner H (2013) Vitamin D receptor polymorphism and colorectal cancer-specific and all-cause mortality. Cancer Epidemiol 37(6):905–907
45. Pineda Lancheros LE, Ramirez P, Sanchez Martin C, Galvez Navas A, Martinez JMM, Ramirez Tortosa F, M. d. C., Morales J, A (2021) Impact of genetic polymorphisms on the metabolic pathway of vitamin D and survival in non-small cell lung cancer. Nutrients 13(11):3783
46. Polly P, Tan TC (2014) The role of vitamin D in skeletal and cardiac muscle function. Front Physiol 5:145
47. Raljević D, Peršić V, Markova-Car E, Cindrić L, Miškulin R, Žuvić M, Kraljević Pavelić S (2021) Study of vitamin D receptor gene polymorphisms in a cohort of myocardial infarction patients with coronary artery disease. BMC Cardiovasc Disord 21(1):188
48. Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS (2012) The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. Endocr Rev 33(3):456–492
49. Saini A, Björkhem-Bergman L, Boström J, Lilja M, Melin M, Olsson K, Ekström L, Bergman P, Altun M, Rullman E (2019) Impact of vitamin D and vitamin D receptor TaqI polymorphism in primary human myoblasts. Endocr Connections 8(7):1070–1081
50. Salles J, Chanet A, Giraudet C, Patrac V, Pierre P, Jourdan M, Luiking YC, Verlaan S, Migné C, Boirie Y (2013) 1, 25 (OH) 2-vitamin D 3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through A kt/PKB and m TOR mediated pathways in murine C 2 C 12 skeletal myotubes. Mol Nutr Food Res 57(12):2137–2146
51. Sandgren ME, Brönnegärd M, DeLuca HF (1991) Tissue distribution of the 1, 25-dihydroxyvitamin D3 receptor in the male rat. Biochem Biophys Res Commun 181(2):611–616
52. Saponaro F, Saba A, Zucchi R (2020) An update on vitamin D metabolism. Int J Mol Sci 21(18):6573
53. Şerifoğlu L, Yılmaz SG, Karaaslanlı A, Düzkalır AH, Etli MU, Özdoğan S (2024) Association of TaqI (rs731236) Polymorphism of Vitamin D Receptor Gene with Lumbar Degenerative Disc Disease. *World Neurosurgery*, *188*, e419-e423
54. Silva AL, Santos J, Tavares V, Ferreira T, Dias V, da Silva C, e Silva M, Medeiros R (2024) The association of the Prognostic Nutritional Index (PNI) and Neutrophil-Lymphocyte Ratio (NLR) with cachexia in cancer patients. Clin Nutr ESPEN 63:1052
55. Silva H-H, Tavares V, Silva M-RG, Neto BV, Cerqueira F, Medeiros R (2022) FAAH rs324420 Polymorphism Is Associated with Performance in Elite Rink-Hockey Players. Biology 11(7):1076
56. Taşkın E, Coşkun M (2025) Are vitamin D receptor gene rs731236, rs2228570 and NOS3 gene rs3138808 polymorphisms associated with diabetic retinopathy? Ophthalmic Genet, 1–7

57. Tavares V, Assis J, Pinto R, Freitas-Silva M, Medeiros R (2023) Venous thromboembolism-related genetic determinant F11 rs4253417 is a potential prognostic factor in ischaemic stroke. Mol Cell Probes 70:101917
58. Tentolouris N, Achilla C, Anastasiou IA, Eleftheriadou I, Tentolouris A, Basoulis D, Kosta O, Lambropoulos A, Yavropoulou MP, Chatzikyriakidou A (2024) The association of vitamin D receptor polymorphisms with COVID-19 severity. Nutrients 16(5):727
59. Tomei S, Singh P, Mathew R, Mattei V, Garand M, Alwakeel M, Sharif E, Khodor A, S (2020) The role of polymorphisms in vitamin D-related genes in response to vitamin D supplementation. Nutrients 12(9):2608
60. Voltan G, Cannito M, Ferrarese M, Ceccato F, Camozzi V (2023) Vitamin D: An overview of gene regulation, ranging from metabolism to genomic effects. Genes 14(9):1691
61. Walsh S, Ludlow AT, Metter EJ, Ferrucci L, Roth SM (2016) Replication study of the vitamin D receptor (VDR) genotype association with skeletal muscle traits and sarcopenia. Aging Clin Exp Res 28(3):435–442
62. Wang P, Ma L, Wang H, Zhang W, Tian Q, Cao D, Zheng G, Sun Y (2006) Association between polymorphisms of vitamin D receptor gene ApaI, BsmI and TaqI and muscular strength in young Chinese women. Int J Sports Med 27(03):182–186
63. Wang X, Shen N, Lu Y, Tan K (2019) Vitamin D receptor polymorphisms and the susceptibility of Parkinson's disease. Neurosci Lett 699:206–211
64. Wang Y, DeLuca HF (2011) Is the vitamin D receptor found in muscle? Endocrinology 152(2):354–363
65. Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L (2013) Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. J Clin Endocrinol Metabolism 98(9):3821–3828
66. Wu J, Chi J, Zhang Y (2025) Vitamin D and cancer-related fatigue in elderly patients: mechanisms and therapeutic insights—a narrative review. Front Nutr 12:1642166
67. Xu X, Shen M (2019) Associations between vitamin D receptor genetic variants and tuberculosis: a meta-analysis. Innate Immun 25(5):305–313
68. Yang C, Li Y (2026) VDR Gene Polymorphisms and Inter-Individual Variability in Response to Resistance Training. Genes 17(2):137
69. Yang W, Huang J, Wu H, Wang Y, Du Z, Ling Y, Wang W, Wu Q, Gao W (2020) Molecular mechanisms of cancer cachexia-induced muscle atrophy. Mol Med Rep 22(6):4967–4980
70. Yates AD, Austine-Orimoloye O, Azov AG, Barba M, Barnes I, Barrera-Enriquez VP, Becker A, Bennett R, Berry A, Bhai J (2026) Ensembl 2026. Nucleic Acids Res 54(D1):D1053–D1060
71. Yu Z-H, Chen M, Zhang Q-Q, Hu X (2018) The association of vitamin d receptor gene polymorphism with lung cancer risk: an update meta-analysis. Comb Chem High Throughput Screen 21(10):704–710

72. Zeng Z, Bromberg Y (2019) Predicting functional effects of synonymous variants: a systematic review and perspectives. Front Genet 10:914
73. Zhang Q, Song MM, Zhang X, Ding JS, Ruan GT, Zhang XW, Liu T, Yang M, Ge YZ, Tang M (2021) Association of systemic inflammation with survival in patients with cancer cachexia: results from a multicentre cohort study. J Cachexia Sarcopenia Muscle 12(6):1466–1476
74. Zhao G, Simpson RU (2010) Membrane localization, Caveolin-3 association and rapid actions of vitamin D receptor in cardiac myocytes. Steroids 75(8–9):555–559

Figures

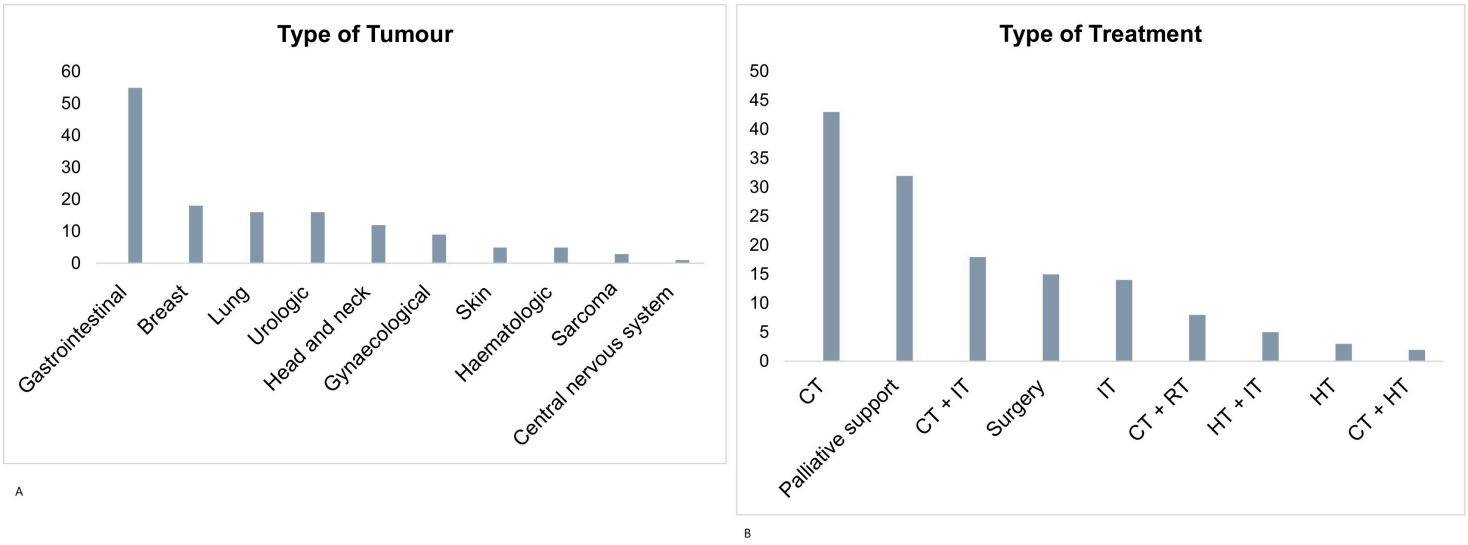

Figure 1

Distribution of malignant disease types **(a)** and cancer treatments **(b)** in the Study Cohort. Abbreviations: CT, chemotherapy; HT, hormonotherapy; IT, immunotherapy; RT, radiotherapy.

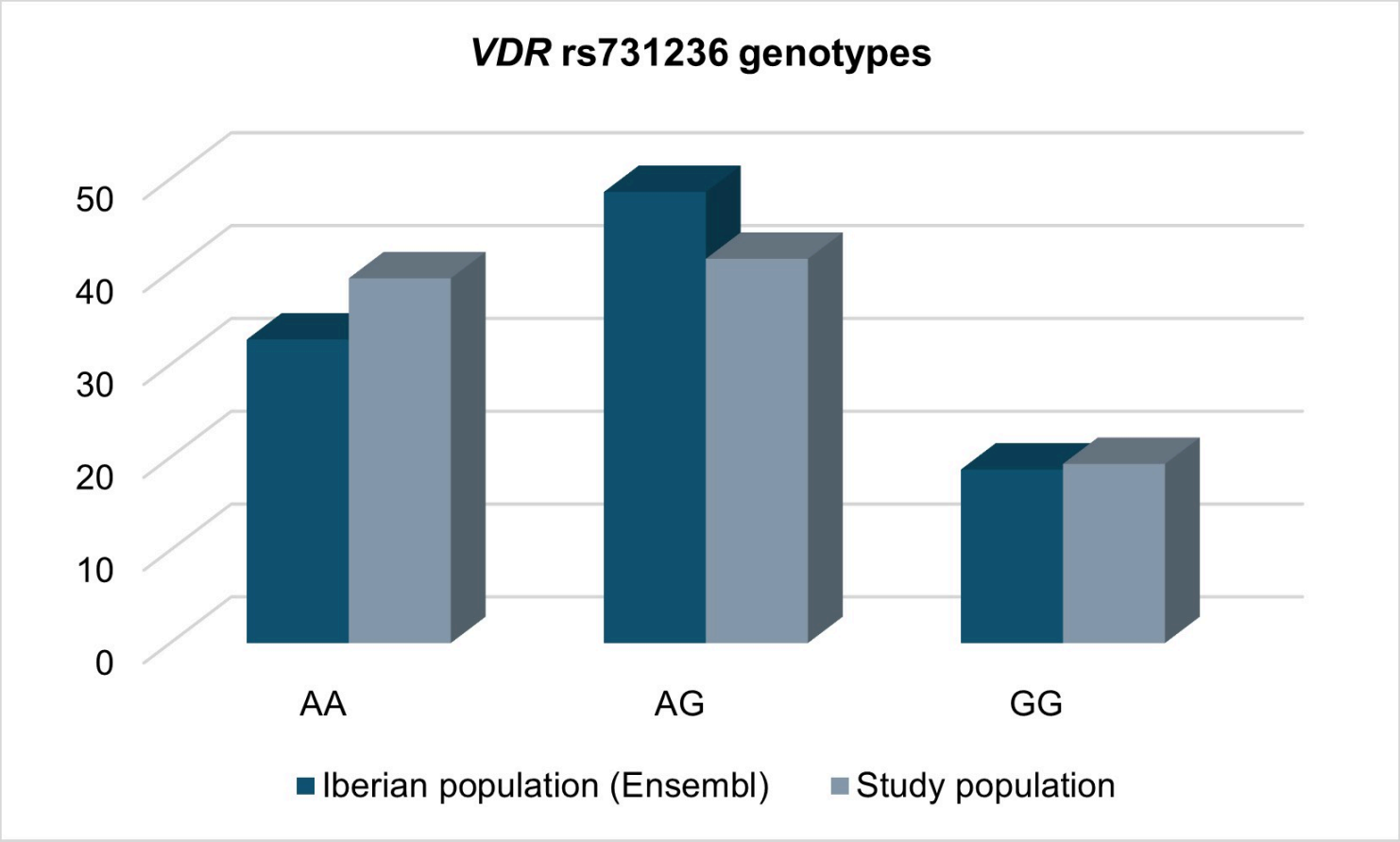

Figure 2

Genotype distribution in the study cohort compared with the reference Iberian population (https://www.ensembl.org/index.html, last accessed on the 28th of December of 2025).

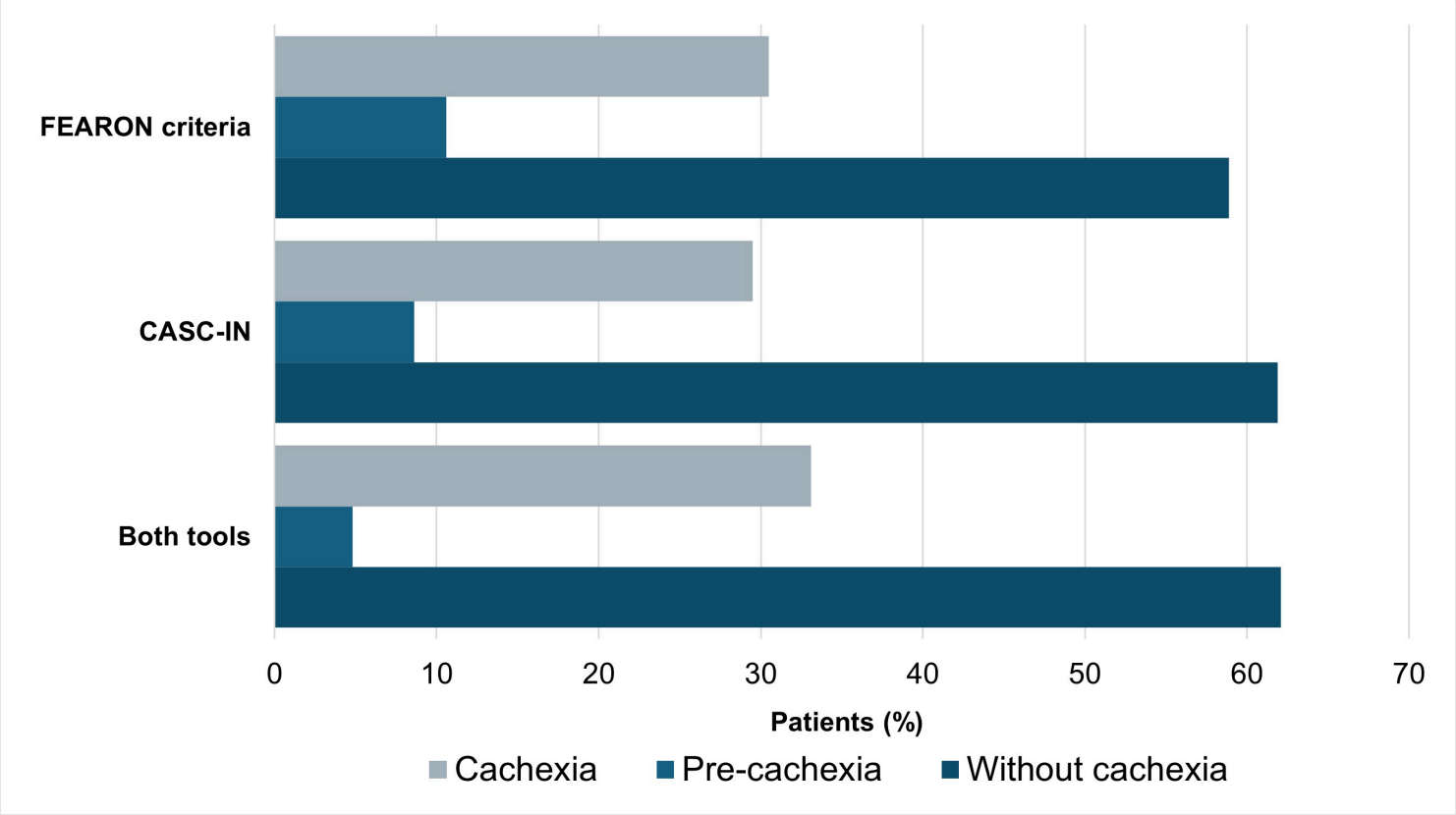

Figure 3

Cachexia prevalence according to each diagnostic approach.

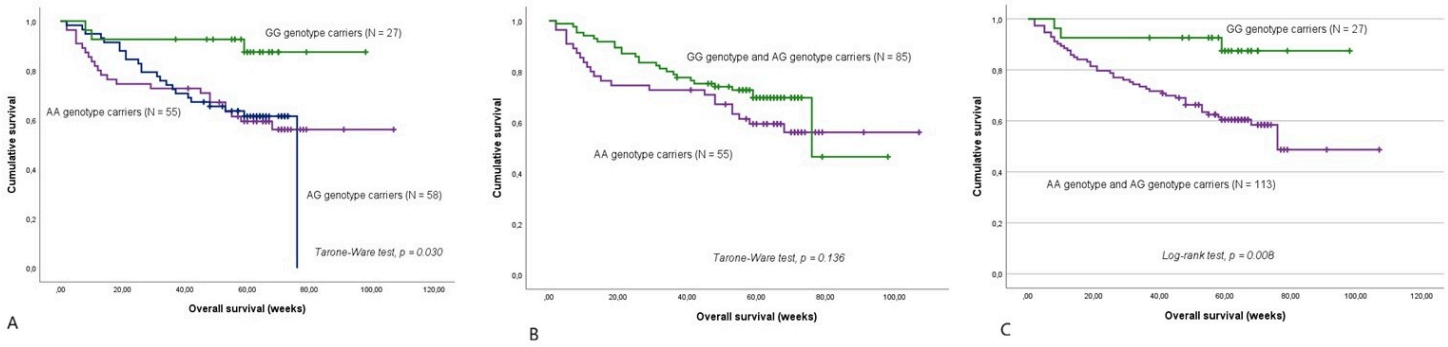

Figure 4

Overall survival (OS) according to *VDR* rs731236 genotypes. **a)** In the addictive genetic model, patients with the GG genotype had significantly higher survival time compared to AA and AG genotype carriers (mean OS = 89.4 ± 4.8 weeks, 71.9 ± 5.8 weeks and 57.6 ± 3.4 weeks; Tarone-Ware test, p = 0.030). **b)** In the dominant genetic model, no significant differences in survival time were observed (Tarone-Ware test, p = 0.136). **c)** In the recessive genetic model, patients carrying the GG genotype had significantly higher survival time compared to patients with A allele carriers (mean OS = 89.4 ± 4.8 weeks and 71.2 ± 4.6 weeks; Log-rank test, p = 0.008).

Supplementary Files

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- Supplementaryfile.xlsx