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ORIGINAL ARTICLE

Phenotypic and genotypic spectrum of a cohort of patients diagnosed with Li-Fraumeni syndrome in the Zona da Mata Mineira and Southern Fluminense macroregion

Espectro fenotípico e genotípico de uma coorte de pacientes diagnosticados com a síndrome de Li-Fraumeni na Zona da Mata Mineira e macrorregião Sul Fluminense

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ABSTRACT

Li-Fraumeni Syndrome (LFS) is a rare hereditary condition characterized by a predisposition to the development of multiple types of cancer, including breast cancer, central nervous system tumors, sarcomas, and leukemias. This syndrome is caused by pathogenic variants in the *TP53* gene, autosomal dominant inheritance, and has high penetrance. This study aims to investigate the phenotypic and genotypic spectrum of a cohort of patients diagnosed with LFS in the Zona da Mata Mineira and Southern Fluminense macroregions. This is a retrospective, observational study that included patients with a confirmed diagnosis of LFS. Data were collected through a review of medical records. This study provided a better understanding of the phenotypic and genotypic characteristics of this specific population, contributing to more accurate and personalized diagnoses, as well as promoting awareness and the development of specialized follow-up in LFS.

Keywords: Li-Fraumeni syndrome; Healthcare team; Oncogenetics.

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None.

RESUMO

A Síndrome de Li-Fraumeni (LFS) é uma condição hereditária rara caracterizada por predisposição ao desenvolvimento de múltiplos tipos de câncer, incluindo câncer de mama, tumores do sistema nervoso central, sarcomas e leucemias. Essa síndrome é causada por variantes patogênicas no gene *TP53*, com herança autossômica dominante e alta penetrância. Este estudo tem como objetivo investigar o espectro fenotípico e genotípico de uma coorte de pacientes diagnosticados com LFS na Zona da Mata Mineira e Macrorregião Sul Fluminense. Trata-se de um estudo observacional retrospectivo que incluiu pacientes com diagnóstico confirmado de LFS. Os dados foram coletados por meio da revisão de prontuários médicos. Este estudo proporcionou uma melhor compreensão das características fenotípicas e genotípicas dessa população específica, contribuindo para diagnósticos mais precisos e personalizados, além de promover a conscientização e o desenvolvimento de um acompanhamento especializado na LFS.

Palavras-chave: Síndrome de Li-Fraumeni; Equipe de saúde; Oncogenética.

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Introduction

Approximately 10% of all cancers are associated with a hereditary predisposition syndrome involving germline variants in DNA repair genes, oncogenes, or tumor suppressor genes[1]. Carriers have a higher risk than the general population of developing cancers throughout their lives[1,2]. One example of this spectrum is Li-Fraumeni Syndrome (LFS), which is associated with germline variants in the *TP53* gene and follows an autosomal dominant inheritance pattern[3]. First described in 1969 by Li and Fraumeni, this syndrome is characterized by a hereditary predisposition to breast cancer, central nervous system tumors, bone and soft tissue sarcoma, adrenal carcinoma, and leukemia, among others[4].

Pathogenic or likely pathogenic germline variants in the gene *TP53* have high penetrance[5,6]. It is estimated that carriers have up to 90% risk of developing cancer by the age of 69 years, and that 50% of cancers occur before the age of 40 [(5)]. Penetrance is higher in women, due to the increased risk of breast cancer associated with the syndrome[6].

Some criteria for suspecting LFS have already been established, such as the classic criteria: a patient with sarcoma under the age of 45; a first- or second-degree relative with cancer under the age of 45; or sarcoma at any age. It is estimated that 70% to 80% of patients who meet the classic criteria have a pathogenic variant in the *TP53* gene, and there is no association of variants in other genes with the Li-Fraumeni syndrome phenotype, with variants in the *TP53* gene remaining the causal variants for the syndrome spectrum[7].

The population diagnosed with LFS in the South and Southeast regions of Brazil has particular characteristics. This population carries a founder mutation (p.R337H) with a high prevalence (0.3%), resulting from a founder effect related to the movement of the Tropeiros in Brazilian territory[8,9]. However, it is estimated that 7 to 20% of Li-Fraumeni Syndrome cases arise due to a *de novo* variant, not inherited from either parent[6].

There are still few studies evaluating patients diagnosed with LFS in the Brazilian population[8,9]. In this study, we evaluated the phenotypic and genotypic profiles of patients diagnosed with Li-Fraumeni Syndrome in a region of Minas Gerais and in the southern area of Rio de Janeiro, aiming to understand specific characteristics of this population and to contribute to a better understanding of issues related to diagnosis, management, family genetic counseling, and the development of specialized services to meet the needs of these patients.

Methods

This study is an observational, cross-sectional research conducted at a private outpatient clinic located in Minas Gerais from January 2020 to December 2024. The target population consists of 21 individuals with molecular confirmation of the syndrome, characterized by the presence of a pathogenic or likely pathogenic variant in the *TP53* gene. The diagnosis was established based on the Chompret criteria[10,11].

Chompret Criteria

1. "Individual with a tumor belonging to the LFS spectrum (sarcoma, brain tumor, adrenocortical carcinoma, or early-onset breast cancer) before the age of 46, and at least one first- or second-degree relative with a tumor within the syndrome spectrum before the age of 56, or with multiple tumors; or"
2. "Individual with multiple tumors, two of which belong to the LFS spectrum, with the first diagnosed before the age of 46; or"
3. "Patient with adrenocortical carcinoma or choroid plexus tumor, regardless of family history."

Patients who met the clinical criteria but did not present pathogenic, likely pathogenic, or variants of uncertain significance (VUS) variants in molecular tests were excluded from the sample.

Molecular testing was performed in certified commercial laboratories that follow internationally recommended quality protocols[12]. The analyses involved multigene panels for hereditary cancer predisposition, including the *TP53* gene, in accordance with laboratory quality guidelines[13]. Genomic DNA sequencing of the target regions utilized Illumina technology. Target regions were sequenced with a depth ≥50x or were supplemented with additional analyses, achieving an average coverage of 173.92x and >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15 bp in length, and exon-level deletions and duplications[12,13].

Patients included in this study who presented pathogenic, likely pathogenic, or variants of uncertain significance (VUS) in other genes in their molecular testing results had these variants described in Table 1.

Variant classification followed the recommendations of the *American College of Medical Genetics and Genomics (ACMG)*[12].

The project was submitted for review by the Ethics Committee of the Federal University of Juiz de Fora, and was approved prior to its implementation (CAAE 85438424.7.0000.547). Data collection began with the search and review of medical records of diagnosed patients. Patients who met the inclusion criteria were invited to participate in the study after signing the informed consent form (Appendix A). Subsequently, data were collected using a structured questionnaire (Appendix B).

The variables studied included:

- Clinical and genetic data: variant identified in the genetic test, age at diagnosis, presence of neoplasia, and type of neoplasia.
- Sociodemographic characteristics: place of origin, ethnicity, age, sex, educational level, and occupation.
- Family history: affected relatives.

A descriptive analysis was conducted using frequency and percentage with the SPSS 20 software.

Results

The sample included 21 individuals, distributed into two age groups: 57.1% of the participants were up to 50 years of age, and 42.9% were over 51 years of age. Information about each individual, such as age, sex, city of origin, observed genetic variant, and variant classification, is presented in Table 1. Participants came from different cities, with Juiz de Fora accounting for the largest proportion (28.5%), followed by Guidoval (14%) and Madre de Deus de Minas (9.5%), while the remaining participants (48%) were from other locations. The majority were female (90.5%) (Tables 1 and 2).

Regarding self-declared race/color, the white population predominated (76.2%), followed by mixed race (14.3%), and black (9.5%) (Table 2). Concerning the education level, 52.3% of the participants had completed higher education, while 9.5% had completed elementary school, and another 9.5% had completed high school, and 28.7% did not provide information regarding their education, as described in Table 1.

The molecular analysis identified different genetic variants. The most prevalent variant was *TP53*:c.1010G>A (p.Arg337His), present in 80.9% of cases. Other variants detected included *TP53*:c.467G>A (p.Arg156His) (9.5%), *TP53*:c.375+1G> (4.8%), and *TP53*:c.818G>A (p.Arg273His) (4.8%) (Table 2). The variant *TP53*:c.467G>A (p.Arg156His), observed in F18, was initially classified as VUS, but was reclassified as likely pathogenic after internal analysis and interpretation according to the ACMG guidelines. All other variants in the *TP53* gene were pathogenic. Some patients (F6, F11, F13, F14, F15, F19, F20, and F21), in addition to harboring a pathogenic variant in the *TP53* gene, also presented variants in other genes classified as variants of uncertain clinical significance (VUS), which are not currently considered to have clinical relevance for the present phenotype.

Regarding clinical history, 52.4% of participants had been diagnosed with breast cancer. In addition, 19% reported a family history of breast cancer, 4.8% of ovarian cancer, and 4.8% of prostate cancer. Another 19% were asymptomatic at the time of evaluation, as shown in Table 2.

Discussion

The results of this study provide valuable insights into the phenotypic and genotypic profiles of patients diagnosed with Li-Fraumeni Syndrome (LFS) in a specific region of Brazil. These findings corroborate aspects previously described in both international and national literature, while highlighting regional particularities that should be considered in the clinical management and genetic counseling of these patients.

The cohort analysis revealed a total of 21 individuals from 15 distinct families, with most patients belonging to separate family units. This highlights a significant dispersion of cases across unrelated lineages, emphasizing the critical importance of raising awareness and providing comprehensive genetic counseling for all family members identified with pathogenic *TP53* variants, given the high penetrance and clinical relevance of these findings.

Table 1. Individual characteristics of participants diagnosed with Li-Fraumeni Syndrome, including clinical, genetic, and sociodemographic data

INDIVIDUAL	AGE (years)	MOLECULAR RESULTS	CRITERIA ACMG – *TP53* VARIANTS	VARIANT CLASSIFICATION	SYMPTOMATOLOGY	EDUCATION LEVEL	RACE/ COLOR	SEX	CITY OF ORIGIN	FAMILIAL RELATIONSHIP
F1	57	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	BREAST CANCER	NR	BLACK	FEMALE	LARANJEIRAS	
F2	61	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	BREAST CANCER	NR	WHITE	FEMALE	MENDES PIMENTEL	Mother of F4
F3	68	*TP53*:c.467G>A (p.Arg156His)	PS4_Moderate, PM2, PM5, PM1	LIKELY PATHOGENIC	OVARIAN CANCER	NR	BLACK	FEMALE	LEOPOLDINA	
F4	32	*TP53*:c.1010G>A (p.Arg337His)	PM2,PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	FAMILY HISTORY OF BREAST CANCER	NR	WHITE	FEMALE	MENDES PIMENTEL	Son of F2
F5	45	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	BREAST CANCER	HIGHER EDUCATION	WHITE	FEMALE	UBÁ	
F6	66	*TP53*:c.1010G>A (p.Arg337His) , *AXIN2*:c.145A>C (p.Met49Leu) *FLCN*:c.65C>T (p.Thr22Met) *MSH3*:c.1777C>T (p.Arg593Trp)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS VUS VUS	BREAST CANCER	HIGH SCHOOL	WHITE	FEMALE	MADRE DE DEUS DE LIMA	
F7	26	*TP53*:c.375+1G>T;(p.?)	PVS1, PM2	PATHOGENIC	BREAST CANCER	HIGHER EDUCATION	WHITE	FEMALE	ITAPERUNA	
F8	45	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	BREAST CANCER	HIGHER EDUCATION	WHITE	FEMALE	JUIZ DE FORA	
F9	47	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	FAMILY HISTORY OF BREAST CANCER	HIGH SCHOOL	MIXED	FEMALE	GUIDOVAL	Sister of F10 and F11
F10	59	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	FAMILY HISTORY OF BREAST CANCER	HIGHER EDUCATION	MIXED	FEMALE	GUIDOVAL	Sister of F9 and F11
F11	58	*TP53*:c.1010G>A (p.Arg337His) *ALK*:c.1100C>G (p.Pro367Arg) *RECQL4*:c.157G>A (p.Gly53Ser)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS VUS	BREAST CANCER	HIGHER EDUCATION	MIXED	FEMALE	GUIDOVAL	Sister of F9 and F10
F12	33	*TP53*:c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	FAMILY HISTORY OF BREAST CANCER	HIGHER EDUCATION	WHITE	MALE	MADRE DE DEUS DE LIMA	

continue...

... continuation Table 1

INDIVIDUAL	AGE (years)	MOLECULAR RESULTS	CRITERIA ACMG – *TP53* VARIANTS	VARIANT CLASSIFICATION	SYMPTOMATOLOGY	EDUCATION LEVEL	RACE/ COLOR	SEX	CITY OF ORIGIN	FAMILIAL RELATIONSHIP
F13	58	*TP53:*c.1010G>A (p.Arg337His) *MUTYH:*c.734G>A (p.Arg245His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS	PROSTATE CANCER	HIGHER EDUCATION	WHITE	MALE	JUIZ DE FORA	Father of F14
F14	19	*TP53:*c.1010G>A (p.Arg337His) *MUTYH:*c.734G>A (p.Arg245His), heterozygous	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC PATHOGENIC	ASYMPTOMATIC	ELEMENTARY SCHOOL	WHITE	FEMALE	JUIZ DE FORA	Daughter of F13
F15	27	*TP53:*c.818G>A (p.Arg273His) *PALB2:*c.3251C>T (p.Ser1084Leu)	PS3, PS4, PM2	PATHOGENIC VUS	BREAST CANCER	HIGHER EDUCATION	WHITE	FEMALE	UBA	
F16	36	*TP53:*c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	BREAST CANCER	NR	WHITE	FEMALE	BOCAINA DE MINAS	
F17	47	*TP53:*c.1010G>A (p.Arg337His)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC	ASYMPTOMATIC	NR	WHITE	FEMALE	UBÁ	
F18	67	*TP53:*c.467G>A (p.Arg156His)	PS4_Moderate, PM2, PM5, PM1	LIKELY PATHOGENIC	BREAST CANCER	ELEMENTARY SCHOOL	WHITE	FEMALE	MURIAE	
F19	25	*TP53:*c.1010G>A (p.Arg337His) *ATM:*c.6255T>A (p.Asp2085Glu)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS	ASYMPTOMATIC	HIGHER EDUCATION	WHITE	FEMALE	JUIZ DE FORA	Daughter of F21 and niece of F20
F20	50	*TP53:*c.1010G>A (p.Arg337His) *ATM:*c.6255T>A (p.Asp2085Glu)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS		HIGHER EDUCATION	WHITE	FEMALE	JUIZ DE FORA	Aunt of F19
F21	58	*TP53:*c.1010G>A (p.Arg337His) *ATM:*c.6255T>A (p.Asp2085Glu)	PM2, PS4, PP1_ Strong, PP3, PM5.	PATHOGENIC VUS	BREAST CANCER	HIGHER EDUCATION	WHITE	FEMALE	JUIZ DE FORA	Mother of F19

Caption: VUS = Variants of uncertain significance; NR = Not reported.

Source: Authors, 2025.

Table 2. Distribution of the study population according to their sociodemographic and clinical characteristics (21).

Sociodemographic-clinical characteristics	N	%
Age group		
≤49 years	12	57.1
≥50 years	9	42.9
Race		
White	16	76.2
Mixed	3	14.3
Black	2	9.5
Sex		
Female	19	90.5
Male	2	9.5
City of Origin		
Guidoval	3	14
Juiz de Fora	6	28.5
Madre de Deus de Lima	2	9.5
Others	10	48
Symptomatology		
Asymptomatic	4	19
Breast cancer	11	52.4
Ovarian cancer	1	4.8
FH of breast cancer	4	19
Prostate cancer	1	4.8
Molecular results		
TP53:c.467G>A (p.Arg156His)	2	9.5
TP53:c.1010G>A (p.Arg337His)	17	80.9
TP53:c.375+1G>	1	4.7
TP53:c.818G>A (p.Arg273His)	1	4.7

Source: Authors, 2025.

However, it was observed that this awareness and follow-up were limited, as in many families, only one or two members underwent genetic testing and appropriate monitoring. The lack of a systematic and integrated approach to family screening hinders the early identification of at-risk, asymptomatic individuals, thereby reducing timely opportunities for preventive intervention.

The predominance of female participants (90.5%) aligns with studies indicating higher penetrance of LFS in women, particularly due to the increased risk of breast cancer[14]. However, this finding may also be related to the fact that women, in general, seek healthcare services more frequently and participate more often in screening programs, which may have influenced the sample composition[15]. Studies such as those by Siegel et al. (2014)[6] confirm that women carrying pathogenic variants in the *TP53* gene have a significantly higher risk of developing neoplasms compared to men. This predisposition highlights the need for specific screening protocols for this group, including annual magnetic resonance imaging, as recommended by sources such as the Toronto Protocol[16,17] and by the NCCN Guidelines[18].

Ovarian cancer is highly prevalent in the general population, but is not directly associated with LFS[19]. However, as more families with *TP53* mutations are identified, the LFS cancer spectrum has expanded to include other cancer types that were initially not associated, such as melanoma, lung, gastrointestinal tract, thyroid, ovarian, and other malignancies[19,20]. In the case of Patient F3, no additional pathogenic variants or VUS were detected that could influence the observed phenotype. In other cases, however, the presence of VUS was observed in addition to the *TP53* variant. In these cases, the potential influence of VUS on the phenotype cannot be completely ruled out, even though a definitive diagnosis cannot be established at this time.

Another relevant finding was the racial distribution of the sample, in which 76.2% of participants identified as white, followed by mixed-race (14.3%) and black individuals (9.5%). This profile may reflect both the demographic composition of the studied region and historical inequalities in access to healthcare services and genetic testing in Brazil. As highlighted by Achatz and Zambetti (2016)[8], the high prevalence of the p.R337H founder mutation in the population of European descent is directly related to the founder effect promoted by the Tropeiros during the country's colonization.

The ages of patients at the time of diagnosis ranged from 18 to 67 years, with a mean of 45.67 years. This

finding is consistent with previous studies reporting that approximately 50% of cancers associated with LFS occur before the age of 40, although a significant proportion is also diagnosed in later adulthood[5]. These data reinforce the need for continuous surveillance of *TP53* mutation carriers, regardless of age, as the risk of developing neoplasms persists throughout life.

The high frequency of the p.R337H founder mutation among participants (80.9%) is consistent with previous studies conducted in Brazil. Achatz and Zambetti (2016)[8] and Garritano et al. (2010)[9] described that this mutation is particularly prevalent in the southern and southeastern regions of the country due to historical factors. Additionally, the presence of *de novo* variants in a small proportion of patients corroborates estimates indicating that 7-20% of LFS cases result from non-inherited mutations[5]. This finding underscores the need for genetic evaluation in patients without a significant family history, particularly in cases that meet the clinical criteria for LFS.

The pathogenic variant in the *MUTYH* gene c.734G>A (p.Arg245His) was observed in the F14 individual in heterozygosity. It is estimated that approximately 1% to 2% of individuals of white European ancestry are heterozygous carriers of a pathogenic variant in the *MUTYH* gene[21]. Although homozygous variants in *MUTYH* cause *MUTYH*-associated polyposis and a greatly increased risk of colorectal cancer, heterozygous carriers are typically asymptomatic, and the increased risk for cancer remains controversial[22-24]. Some studies have associated the presence of heterozygous variants in *MUTYH* with a predisposition to colorectal cancer later in life[23]. However, large population analyses have not demonstrated a significant association with the risk of colorectal, breast, or endometrial cancer[24]. Thus, the presence of this variant probably does not explain the phenotype of individual F14, and there is no known association between variants in the *MUTYH* gene and the phenotype of Li-Fraumeni syndrome, whose manifestations continue to be attributed to variants in *TP53*.

Although LFS is a condition widely described in populations from different parts of the world, some particularities observed in the Brazilian context are noteworthy. The p.R337H variant, practically exclusive to the Brazilian population and rarely reported in other countries, reinforces the relevance of regional studies for understanding the local specificities of LFS. Furthermore, access to diagnosis and follow-up remains unequal in the country, often limited to specialized centers, which limits adequate management and highlights the need for public policies that expand genetic counseling and screening[25]. Despite the contributions of this study to the characterization of the phenotypic and genotypic profile of LFS in this population, important gaps remain, such as the absence of data on the predicted impact of p.R337H, and the need for longitudinal and multicenter studies that include other Brazilian regions. Finally, ensuring greater access to molecular diagnosis and specialized follow-up is fundamental to improving clinical advances and promoting equity in care, bearing in mind that even individuals with negative results or VUS should remain under follow-up, when they meet the clinical criteria, due to the constant evolution of genomics.

Conclusion

This study provides significant insights into the phenotypic and genotypic characteristics of patients diagnosed with Li-Fraumeni Syndrome (LFS) in the Zona da Mata Mineira and Southern Fluminense macroregions. The findings corroborate previous studies, while also highlighting regional particularities that influence clinical management and genetic counseling of affected individuals.

A key finding of this study is the high prevalence of the *TP53* p.R337H founder mutation, reinforcing its strong association with the Brazilian population. This mutation was detected in 80.9% of the cohort, underscoring its historical and genetic significance within the region. The predominance of female patient aligns with existing literature suggesting a higher penetrance of LFS in women, particularly due to the elevated risk of breast cancer. These findings emphasize the necessity of targeted surveillance and early detection programs for individuals carrying this mutation.

Most participants had a personal history of cancer with symptomatology, and breast cancer being the most frequent diagnosis. This pattern reinforces the importance of genetic counseling and continuous monitoring in at-risk families.

The study also revealed potential disparities in access to genetic testing and healthcare services, as reflected by the demographic characteristics of the cohort. While the majority of patients were of European descent, it remains essential to consider the impact of socioeconomic factors on the accessibility of genetic diagnosis and long-term management.

Despite its contributions, this study has certain limitations, including the relatively small sample size and its restriction to a specific geographic region. Further research, including longitudinal studies and larger, more diverse cohorts, is necessary to deepen our understanding of LFS in Brazil. Expanding access to genetic counseling and implementing regional screening programs will be crucial steps toward improving the clinical outcomes of individuals with LFS.

In conclusion, this study enhances our knowledge of LFS in the Brazilian population, providing valuable data that can inform future research, clinical guidelines, and public health initiatives. The findings underscore the importance of continued surveillance, early intervention, and equitable access to genetic testing and specialized care for individuals at risk.

Author's contributions

We describe contributions to the papers using the taxonomy (CRediT) provide above:

Conceptualization, Investigation, Methodology, Visualization & Writing – Review & Editing: LMF Sobrinho; ESK Fernandes; MO Freitas. *Supervision & Writing – Original Draft*: LMF Sobrinho; ESK Fernandes; MO Freitas; LH Laranja; M Prudente; DN Coelho; MPM Estevam; M Prudente. *Validation & Software*: LH Laranja. *Resources & Funding Acquisition*: Not applicable. *Data Curation & Formal Analysis*: MO Freitas.

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