ORIGINAL ARTICLE

Clinic-pathological study of the luminal subtypes in the breast carcinoma

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ABSTRACT

Introduction: the majority of breast carcinomas subtype are positive to the expression of hormone receptors which is associated to a good response to the endocrine therapy.
Objective: to determine the incidence of the luminal subtypes luminal A diagnosed at the Teaching University Hospital Celestino Hernández, Villa Clara and its correlation with classical prognostic value clinic-pathological variables.
Methods: a retrospective, cross-sectional study was carried out at the Hospital Celestino Hernández of the period from January 2017 to June 2019. The research included 281 women with diagnosis of infiltrating breast carcinoma, whose biopsies were studied by immunohistochemistry. It was determined the incidence of the luminal subtypes luminal A and B and their correlation with the variables: age, location, tumor size, histologic type and histologic grade. The proliferation index was determined for luminal B tumors.
Results: the molecular subtype luminal B had a higher incidence. In both luminal subtypes more than two third of patients were older than 50 years old, more than 60 % had no special histology tumors and similar percentage were associated to moderately histological types of breast carcinoma. The poorly-differentiated tumoral lesions and the tumor size larger than 2 cm was reported with higher incidence in luminal B tumors and more than 90 % of tumors of that molecular subtype had a high proliferation index.
Conclusions: the molecular subtype luminal B had clinic and histological features that render a more aggressive biological behavior.
Key words: breast neoplasms; immunohistochemistry study; luminal subtypes

RESUMEN

Introducción: la mayoría de los carcinomas de mama expresan receptores hormonales, lo que traduce una mejor respuesta a la terapia endocrina.
Objetivo: determinar la incidencia de los subtipos luminales en los carcinomas mamarios diagnosticados en el Hospital "Celestino Hernández" y su relación con variables clínico-patológicas clásicas de valor pronóstico.
Métodos: estudio retrospectivo, de corte transversal, realizado en el Hospital "Celestino Hernández" en el período comprendido de enero de 2017 a mayo de 2019.

Se incluyeron 281 mujeres con diagnóstico histológico de carcinoma mamario infiltrante y estudio inmunohistoquímico realizado. Se determinó la incidencia de los subtipos luminales A y B y la relación de cada uno con las variables: edad, talla tumoral, tipo y grado histológicos. Se determinó el índice de proliferación para los tumores luminal B.
Resultados: el subtipo molecular luminal B del carcinoma mamario tuvo una mayor incidencia. En ambos subtipos luminales más de las dos terceras partes de las pacientes fueron mayores de 50 años, más del 60% tuvieron histología no especial y similar proporción estuvieron asociadas a variantes histológicas moderadamente diferenciadas del carcinoma mamario. Las lesiones poco diferenciadas y las tallas mayores de 2 cm se informaron con mayor incidencia en el subtipo luminal B y más del 90% de los tumores con ese subtipo molecular presentaron un índice de proliferación elevado. Hubo asociación estadísticamente significativa entre el grado tumoral y los subtipos moleculares.
Conclusiones: el subtipo molecular luminal B presentó características clínicas e histopatológicas que traducen un comportamiento biológico más agresivo.
Palabras clave: neoplasia de la mama; estudio inmunohistoquímco; subtipos luminales

INTRODUCCIÓN

Breast cancer is the second most frequent neoplasm in the world and the most frequent in women, which is why it is considered an important health problem both in developed countries and in third world nations, with an annual incidence of more than 1,000,000 new cases.[1,2,3]
According to statistics from the GLOBOCAN project, an initiative of the International Agency for Research on Cancer (IARC), in 2020 breast cancer was the most common malignancy worldwide (excluding non-melanocytic skin cancer) and was, at the same time, the most frequent in women, with an estimated 2 261 419 cases of breast cancer diagnosed (24.5% of all cancers in women) and caused 6.9% of cancer deaths in women, making it the fourth most common cancer in women, preceded only by malignant tumors of the lung, liver and stomach. The worldwide incidence of breast cancer is 47.8% cases per 100 000 women.[4]
In Cuba, according to the statistical yearbook for the year 2021, the incidence of cancer in women was localized, in the first place, in the skin, and in the second place in the breast, with 3,886 new cases. In terms of mortality, breast cancer ranked second in the female sex, with a rate of 30.4 per 100,000 women, and was displaced only by trachea, bronchus and lung tumors (rate of 38.1 per 100,000 female population).[5]
Breast cancer is a group of tumors with a very diverse biological behavior and great clinical variability. In the anatomopathological diagnosis of these neoplasms, the histological classification based on morphology has traditionally been used, in which ductal carcinoma is the most common variant;[6] however, the current histological classification does not reflect the heterogeneity of the tumors in their biological behavior, nor does it allow the identification of patients who will present better responses and benefits with the different therapeutic modalities. It is currently assumed that the clinical and prognostic diversity of mammary carcinomas that are similar and homogeneous in their morphology and classic prognostic factors is established at the molecular level by expressing different genes that confer variability in this regard.[3,6]

Advances in molecular biological techniques have allowed simplified molecular classification of breast cancer with a panel of immunohistochemical biomarkers. Dozens of markers are currently used in the study of breast neoplasms; however, the best known and most widely used are: estrogen receptors (ER), progesterone receptors (PR), Her2, and Ki-67, which define the treatment and prognosis of the disease.[7]

Estrogen hormone receptors (ER) and progesterone receptors (PR) are G protein-coupled receptors and members of the steroid receptor superfamily. These receptors are activated by binding with high affinity to female sex hormones and, once active, behave as transcription factors by binding to the promoters of target genes at specific binding sites.[8] The determination of these receptors in breast carcinoma has predictive and prognostic value, primarily estrogen receptors as predictive value to anti-estrogen therapy and progesterone receptors as prognostic value.[8,9]

The majority (70-80%) of breast carcinomas express ER and PR and, according to molecular classification, these tumors correspond to the luminal subtype.[8,10] These tumors, in turn, are subclassified into:

- Luminal A: these are tumor lesions with a low cell proliferation index (Ki67). They are positive for hormone receptor expression (ER and PR), but never overexpress the Her2/neu oncogene. They usually have a good prognosis, with a lower incidence of relapse and a higher survival rate. They have a high response rate to hormonal therapy and a more limited benefit with chemotherapy.[10]
- Luminal B: are lesions that in addition to expressing ER and PR (or both) can express the Her2 oncogene. They usually have a high proliferation index (Ki67) and generally express lower levels of PR than tumors with luminal A subtype. They represent the group of luminal tumors with the worst prognosis. They benefit from hormone therapy and to a greater extent from chemotherapy.[8,9,10]

New cases of mammary carcinoma are diagnosed every year at the "Celestino Hernández" Hospital and are subjected to immunohistochemical studies based on the four basic markers: hormone receptors (estrogen and progesterone), Her2 and Ki67.

The present study aimed to determine the incidence of luminal subtypes diagnosed by immunohistochemistry at the Hospital and to determine the relationship of each subtype with other classic clinicopathological variables of prognostic value in breast carcinoma.

MÉTODOS

Design and population

A retrospective, cross-sectional study was carried out at the "Celestino Hernández" University Hospital of Santa Clara City, Villa Clara Province, from January 2017 to May 2019. The study population consisted of patients with histopathological diagnosis of infiltrating breast carcinoma attended at the hospital institution during that period of time; the biopsies were submitted to immunohistochemical study.

The study did not include patients with:

- Histopathological diagnosis of breast carcinoma "*in situ*" (non-invasive)

- Incomplete immunohistochemical study due to a missing marker at the time of processing or because the tissue sample had some artifact that prevented its adequate study.

Study variables

1. Molecular subtype (immunophenotype): refers to the immunohistochemical profile of each tumor lesion determined through the study of hormone receptors (ER and PR), Her2 and Ki67. In the present study, the molecular subtypes of breast carcinoma positive for hormone receptor expression (luminal subtypes) were evaluated and classified according to the 2015 Saint Gallen criteria[10,11] as follows:

- Luminal A: RE (≥1%), RP (≥20%), Her2 (–) y Ki67<20%
- Luminal B:
  - RE (≥1%), Her2 (+) and any RP y Ki67
  - RE (≥1%), Her2 (-) y Ki67 (≥20%) o RP (<20%).

2. Age: discrete quantitative variable. It is defined as the age in years that each patient presented at the time of diagnosis.

3. Tumor size: continuous quantitative variable. It refers to the size in centimeters of the tumor lesion at the time of diagnosis. It was given in centimeters (cm). Although each lesion was measured in the three dimensions at the time of the anatomopathological study, the largest diameter of each lesion diagnosed was the one taken as reference in this research. In the analysis of tumor size, the following ranges were used, which were taken from the TNM classification of mammary carcinomas:[9]

- less than or equal to 2 cm (≤2 cm)
- greater than 2 and less than or equal to 5 cm (> 2 y ≤ 5 cm)
- greater than 5 cm (> 5 cm).

4. Histologic type: nominal qualitative variable. It refers to the morphological type of the tumor diagnosed by conventional light microscopy. The histology of each tumor lesion diagnosed was determined according to its morphology evaluated with the routine staining technique (hematoxylin-eosin). The current WHO (World Health Organization) classification of 2019 was used.[12]

5. Histologic grade: ordinal qualitative variable. It refers to the degree of differentiation of the tumor. Diagnosed lesions were histologically graded through the Nottingham histological score, which corresponds to the Scarff-Bloom-Richardson grading system, modified by Elston and Ellis. According to this score, tubule formation, nuclear pleomorphism and tumor mitotic count were evaluated. Each variable was identified with a score 1, 2 or 3 and with the sum of these the total histological grade was obtained, according to which grade 1 (total score=3 to 5 points) corresponds to well differentiated tumors with a favorable prognosis; grade 2 (total score=6 to 7 points), to moderately differentiated tumors with an intermediate prognosis and grade 3 (total score=8 to 9 points), corresponds to poorly differentiated tumor lesions, with a more aggressive biological behavior and an unfavorable prognosis.[9,10,13]

6. Cell proliferation index (Ki67): a discrete quantitative variable. It is a way of measuring how fast cancer cells grow and divide. It was studied through immunohistochemistry techniques by determining Ki67 (cell cycle regulatory protein), which has played an important role in tumor classification and,

therefore, is part of the prognostic and predictive factors of mammary carcinomas. High values for Ki-67 mean that many cells are dividing, so that the cancer tends to grow and spread more rapidly.[9]

Data collection and management

The data for the study were obtained from the review of the patients' medical records.

According to the expression of the markers, ER and PR positive tumors were considered to be those with a minimum nuclear staining of 1% of the tumor cells and Her2 positive tumors and when in the immunohistochemical study intense staining was observed at the level of the entire cell membrane surface in more than 30% of the tumor cells (3+).

In the Ki67 assessment, the cut-off point of 20% was established (according to the Expert Consensus for the Treatment of Breast Cancer, Saint Gallen, 2015) below which it was considered low proliferation index and above which high proliferation index.[11,14]

Tumor lesions positive for hormone receptor expression (regardless of labeling intensity) were identified to determine the incidence of luminal subtypes in breast carcinomas diagnosed at the hospital institution during the indicated period. The relationship of each luminal subtype (A and B) with different classic clinicopathological variables of known prognostic value was also determined.

The variables of interest were compiled in a database by computerized methods using Microsoft Excel for Windows version 2016 (16.0), which was also used to perform the calculations and statistical analyses.

Statistical analysis

The distribution of each of the variables was examined individually, tables were used to show the information collected and the data obtained were shown in nominal and percentage expressions.

The mean and standard deviation were calculated for the quantitative variables; in the Ki67 study, the median and range were also calculated.

The Chi-square test was performed in the study of histological grade to determine the association of this variable with the luminal subtypes of mammary carcinoma. Student's t-test was applied to compare mean differences. Statistical significance in both tests was established with a $p<0.05$ value.

Ethical aspects

The study was carried out only with clinical histories from the hospital institution, so there were no ethical conflicts as no patients were directly involved in the research. The anonymity of the identities of the medical records used was guaranteed. Access to the medical records was made with the prior approval and permission of the institution's management.

RESULTS

A total of 281 patients diagnosed with infiltrating breast carcinoma were studied: 47 (16.7%) had tumors with luminal molecular subtype A, 164 (58.4%) were diagnosed with luminal subtype B carcinomas, 22 (7.8%)

corresponded to the Her2/neu subtype and 48 (17.1%) had triple negative tumor lesions. These results show that more than 75% of the breast tumors diagnosed corresponded to luminal subtypes, with the highest incidence for luminal B immunophenotype.

Figure 1 shows that 70.1% of patients with luminal A carcinomas and 78.6% of those with luminal B tumor lesions were over 50 years of age at diagnosis, with the highest incidence in the 51-70 age group for both luminal subtypes. The mean age at presentation was also very similar in both molecular subtypes: 61.32 (±12.73) years in patients with luminal A tumors and 60.73 (±7.78) years in patients with luminal B tumor lesions. There was no statistically significant difference between the mean ages of the two luminal subtypes (p=0.788).

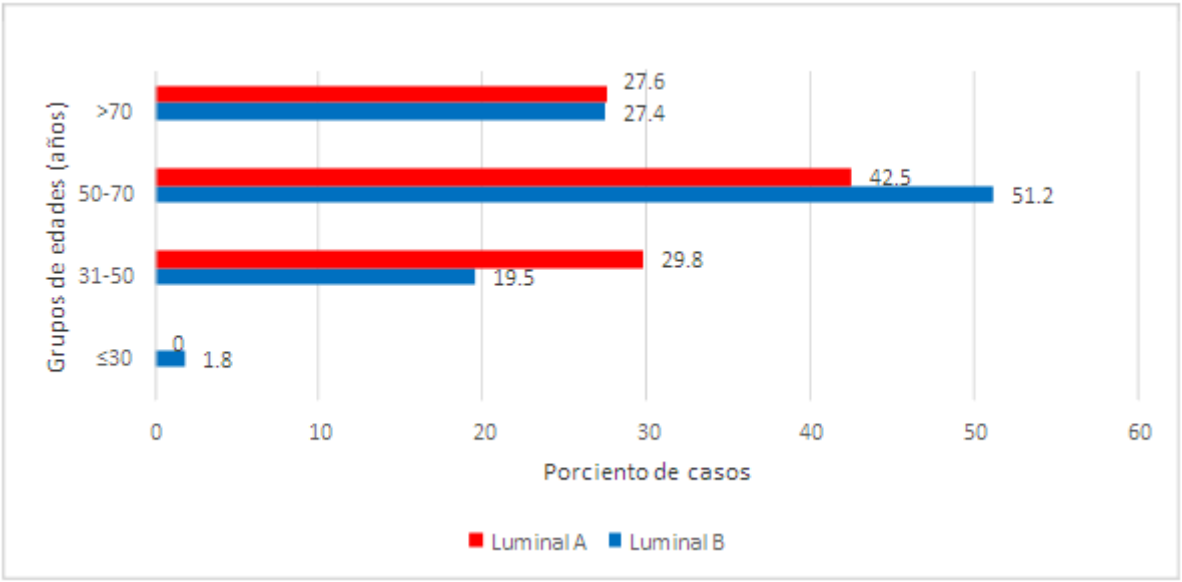

Figure 1. Percentage distribution of luminal subtypes in breast carcinomas by age group

Source: medical records

In relation to tumor size 31 patients (65.96%) with luminal A tumor lesions presented tumor sizes smaller than 2 cm at diagnosis and in 13 (27.66%) tumors larger than two and smaller than 5 cm (> 2 and ≤ 5 cm) were reported. Of the patients with luminal B tumors, 81 (49.39%) had tumor sizes greater than two and less than 5 cm (Table 1). The mean tumor size was 1.97 cm (±0.14) for luminal A subtype and 2.3 (±2.47) cm for luminal B, showing a statistically significant difference (p=0.012) between the two molecular subtypes, with a tendency for luminal B tumors to present larger tumor sizes at diagnosis.

Table 1. Distribution of luminal subtypes A and B in mammary carcinomas according to tumor size (cm)

Tumor size (cm)	Luminal A	%	Luminal B	%
≤ 2	31	65.96	69	42.07
> 2 y ≤ 5	13	27.66	81	49.39
> 5	3	6.38	14	8.54
Total	**47**	**100**	**164**	**100**

Source: medical records

In relation to histologic type, the non-special histologic type (invasive ductal carcinoma) was reported in 29 patients (61.70%) with mammary carcinomas with luminal subtype A and in 135 (82.31%) with luminal B tumors, so there was a significant predominance of this histologic type in both luminal subtypes. The lobular histological type was reported in second place in order of frequency (Table 2).

Table 2. Distribution of luminal subtypes A and B in breast carcinomas according to histological type

Histological type	Luminal A	%	Luminal B	%
Non-special type carcinoma (ductal carcinoma)	29	61.70	135	82.31
Lobular carcinoma	11	23.40	20	12.20
Papillary carcinoma	4	8.51	7	4.27
Mucinous carcinoma	3	6.38	1	0.61
Medullary carcinoma	0	0	1	0.61
Total	**47**	**100**	**164**	**100**

Source: medical records

With respect to histologic grade 35 patients (74.47%) with luminal subtype A had moderately differentiated histologic variants and in 10 (21.28%) moderately differentiated histologic grades were reported. In contrast, in tumor lesions with luminal phenotype B, 109 patients (66.46%) had moderately differentiated lesions and 34 (20.73%) had poorly differentiated lesions (Table 3).

Table 3. Distribution of luminal subtypes A and B in breast carcinomas according to histological grade

Histological grade	Luminal A	%	Luminal B	%	Value of p
Well differentiated (grade 1)	10	21.28	21	12.80	
Moderately differentiated (grade 2)	35	74.47	109	66.46	0.018*
Poorly differentiated (grade 3)	2	4.25	34	20.73	
Total	**47**	**100**	**164**	**100**	

Source: medical records
*When considering (by Pearson's Chi-square test) the variables molecular subtype and histological grade, a statistically significant association was obtained between both variables (p=0.018)

Although a predominance of histological grade 2 (moderately differentiated) was observed in both luminal subtypes, it should be noted that a significant proportion of tumors with luminal subtype B (20.73%) were associated with poorly differentiated histological variants and that well-differentiated lesions were reported in greater proportion in tumors with luminal subtype A (21.28%). The association of histological grade and molecular subtype was statistically significant (p=0.018), which also translates the greater tendency of luminal B tumors to be associated with less differentiated histological variants of mammary carcinoma.

Regarding the tumor proliferation index, lesions with luminal A phenotype have, by concept, a low proliferation index (< 20%); however, luminal B tumors can have a variable proliferation index (high or low). Table 4 represents the

proliferation index of tumor lesions with luminal subtype. It can be seen that 100% of tumors with luminal subtype A had a low proliferation index (< 20%); however, 96.34% of carcinomas with that molecular subtype had high proliferation indices (≥ 20%).
The mean proliferation index obtained was 39% (±7.1%), with a median of 35% and a range between 10 and 90%.

Tabla 4. Distribution of luminal molecular subtype B in mammary carcinomas according to proliferation index

Proliferation rate	Luminal A	%	Luminal B	%
< 20%	47	100	6	3.66
≥ 20%	0	0.00	158	96.34
Total	**47**	**100**	**164**	**100**

Source: medical records and biopsy reports

DISCUSSION

The results obtained in the present investigation show that luminal subtype B was reported with a much higher frequency. These findings are not congruent with the scientific literature consulted,[7,9,10,13] in which it is referred that the luminal subtype A is the molecular subtype that is usually registered with greater frequency (39-67%). In a study carried out in Spain[6] the luminal subtype A presented a frequency of 62.5% (much higher than that obtained in the present study) and the luminal subtype B was reported in 18% of the patients studied. In other investigations, tumor lesions with luminal molecular subtype A also predominated, which were identified in 29.3%[15] and 31%[16] of the patients studied.
In a study conducted in Pakistan and published in 2018[17], 1 224 patients with luminal subtype carcinomas were studied: 845 (69%) had lesions with luminal B phenotype and 379 (31%) were luminal A, thus showing a much higher incidence of tumors with luminal B subtype.
Although the luminal A molecular subtype is usually the most frequent in the different studies, this finding is not always constant. These differences in the incidence of each luminal subtype in the different worldwide investigations may be explained by variations in the genetic expression of mammary carcinoma in different geographic regions.
Regarding age, the results obtained by the authors agree with those of a study[6] in which 74.2% of patients diagnosed with luminal A breast carcinomas and 67.3% of patients with luminal B lesions were also older than 50 years at the time of diagnosis.
Tumors with luminal subtypes also occurred more frequently in patients older than 50 years, with higher incidence in ages between 51 and 70 years;[17] however, the mean ages of the patients studied were lower than those obtained in this investigation, which showed a marked tendency of luminal subtype B to occur in younger patients. From a statistical point of view, this tendency was not significant in the present investigation, but it should be noted that all the patients diagnosed with mammary carcinomas at ages younger than 40 years presented luminal B tumors.

Tumor size is an important prognostic factor because it has a direct association with survival and nodal status in the patient.[9] It has been postulated that carcinomas with luminal B phenotype have a greater expression of proliferation and cell cycle genes,[9,10] and therefore tend to grow faster and present greater tumor size at diagnosis than luminal A lesions. This statement was corroborated by the results obtained in the present study; however, several investigations have obtained different findings. One investigation[6] showed that 67.6% of patients with luminal A tumors and 59.1% of luminal B lesions were less than 2 cm in size, thus showing a predominance of relatively small tumor sizes (< 2 cm) in both luminal subtypes. In another investigation[18] more than 50% of carcinomas of both luminal subtypes had tumor sizes greater than 2 cm at diagnosis.

In relation to histologic subtype, non-special type carcinoma (infiltrating ductal carcinoma) was the predominant histologic type in both luminal subtypes. Infiltrating lobular carcinoma was observed second in order of frequency (23.4% of cases in luminal subtype A and 12.2% of cases in luminal subtype B). Similar results were obtained in other studies[6,18] in which the ductal histologic type was predominantly reported in all molecular subtypes of breast carcinoma; and the lobular histologic type was also reported second in order of frequency, mainly associated with the luminal molecular subtypes (luminal A and B).

This predominance of non-special histology (ductal carcinoma) is explained by the high incidence of that histological type (approximately 80%) within the total number of breast carcinomas diagnosed each year.[7,13,19,20]

Regarding histologic grade, the findings obtained in the present study were concordant with those obtained in previous studies.[17,18] One of these also found a statistically significant association of histologic grade with the molecular subtypes of mammary carcinoma.[17]

Another study conducted in Ecuador[21] also found a greater tendency for luminal B tumors to be associated with poorly differentiated histological variants of breast carcinoma.

The proliferation index determined through the immunohistochemical marker Ki67 is an important prognostic and predictive factor in breast cancer, a very useful criterion for subclassifying luminal subtypes into luminal A and luminal B.[14,19] In luminal A subtype the proliferation index is always low (<20%), but in luminal B with low expression of the progesterone receptor (<20%) or positive for the Her2 oncogene it can have any value.

In this investigation more than 90% of luminal B carcinomas presented high proliferation indices (≥20%). These statistics are higher than those obtained in a study performed in Argentina[22] in which 147 patients with luminal B tumors were studied, of which 66 presented Ki67 levels higher than 20%, representing 44.9%. The median Ki67 expression in that investigation was 25.9%, also lower than that obtained in the present investigation.

The elevated proliferation index in a high proportion of patients with luminal B tumors is also an important indicator of the faster growth rate in this molecular subtype of mammary carcinoma, which translates into a more aggressive biological behavior of the diagnosed lesions and a more unfavorable prognosis.

This research had the limitation of not having all the clinical variables of the patients as it was a retrospective study and not having followed up the patients

to observe survival or response to treatment; however, it is a very useful study in order to achieve a better knowledge about the two most frequent molecular subtypes of mammary carcinoma and their clinicopathological characteristics. This research may serve as a reference for other more extensive research that may be carried out in the future on this very useful and important subject.

CONCLUSIONS

The interpretation of the results of this study leads to the conclusion that the molecular subtypes with the highest incidence in breast carcinoma are luminal, with a higher incidence of luminal B tumors. Luminal subtypes A and B occurred more frequently in women over 50 years of age and were mainly associated with the non-special histological type. Luminal subtype B presented, more frequently, a tumor size greater than 2 cm at the time of diagnosis, showed a greater association with poorly differentiated histological variants of mammary carcinoma and had, in a very high percentage of patients, a high proliferation index, characteristics that translate into a more aggressive biological behavior and an unfavorable prognosis. A statistically significant association was observed between the luminal subtypes of breast carcinoma and the histological grade variable.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTION OF THE AUTHORS

RGP: conceptualization, visualization, formal analysis, research, data curation, writing the original draft and final version of the manuscript.
LlLlG: data curation.
DBG, YAB: formal analysis, methodology, research, writing the original draft.
LSH, AFR: formal analysis, research.