Clinical and Translational Oncology
https://doi.org/10.1007/s12094-020-02396-6

RESEARCH ARTICLE

Dynamic evaluation of neutrophil-to-lymphocyte ratio as prognostic factor in stage III non-small cell lung cancer treated with chemoradiotherapy

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Received: 12 March 2020 / Accepted: 12 May 2020

Abstract

Purpose Locally advanced non-small cell lung cancer (LA-NSCLC) is frequently treated with chemoradiotherapy (CRT). Despite the efforts, long-term outcomes are poor, and novel therapies have been introduced to improve results. Biomarkers are needed to detect early treatment failure and plan future follow-up and therapies. Our aim is to evaluate the role of dynamics of neutrophil-to-lymphocyte ratio (NLR) in patients with locally advanced NSCLC treated with CRT.

Methods We retrospectively reviewed patients diagnosed with LA-NSCLC receiving definitive CRT at our center from 2010 to 2015. Baseline and post-treatment NLR were collected from our center database. NLR was dichotomized (threshold = 4) and patients were divided into two groups based on the variation from baseline to post-treatment NLR. The prognostic role and association with response were examined with logistic regression and multivariate Cox regression model, respectively.

Results Ninety-two patients were included. Our analysis shows that NLR after treatment is associated with response to treatment [OR in the multivariate analysis 4.94 (1.01–24.48); p value = 0.048]. Furthermore, NLR and ECOG are independent prognostic factors for progression-free survival (PFS) and overall survival (OS). Specifically, PFS was 25.79 months for the good prognosis group and 12.09 for the poor prognosis group [HR 2.98 (CI 95% = 1.74–5.10), $p < 0.001$]; and OS was 42.94 months and 18.86 months, respectively [HR 2.81 (CI 95% = 1.62–4.90), $p < 0.001$].

Conclusion Dynamics of NLR have a prognostic value in stage III NSCLC treated with definitive CRT. Pre- and post-CRT NLR should be evaluated in prospective clinical trials involving consolidation treatment with immunotherapy.

Keywords Non-small cell lung cancer · Neutrophil-to-lymphocyte ratio · Stage III · Chemoradiotherapy · Survival outcomes

Introduction

Lung cancer remains the leading cause of cancer-associated death in Western Europe, despite a decline in the incidence of this disease related to a reduction in tobacco use over the past decades [1]. Non-small cell lung cancer (NSCLC) accounts for 80% cases and approximately one-quarter of these patients are diagnosed with locally advanced disease (stage III NSCLC) [2]. Despite the efforts, survival rates still reveal a poor prognosis; specifically, stage III NSCLC 5-year survival rates are around 30% in stage IIIA, 25% in stage IIIB, and only 13% in stage IIIC [3]

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Published online: 24 May 2020

Furthermore, stage III NSCLC includes a heterogeneous group of patients due to the difference in local presentation (high-volume tumors, infiltration of mediastinal structures, and/or nodal involvement). For this reason, treatment decisions represent a challenge for clinicians. Chemoradiotherapy (CRT), either concurrently or sequentially administered, is the standard treatment for unresectable locally advanced NSCLC. The concurrent approach is the preferred treatment because of the demonstrated longer survival, even at the expense of higher rates of toxicity [4], but not all patients benefit from this scheme. Recently, the addition of immunotherapy after CRT has shown improved progression-free survival rates in stage III NSCLC, but long-term survival data are still awaited [5]. Considering this scenario, prognostic and predictive biomarkers to anticipate treatment failure and to identify potential responders and non-responders to therapy are needed.

In this context, the association between cancer prognosis and systemic inflammatory response has been studied in the last years, especially in NSCLC [6, 7]. Among the inflammatory indexes that have been investigated in NSCLC, the most widely recognized as a prognostic factor in advanced disease is the neutrophil-to-lymphocyte ratio (NLR) [8–10]. More recently, the predictive value of NLR was explored in stage IV NSCLC during treatment with nivolumab [11, 12]. Although NLR has also been demonstrated as a prognostic factor in localized and locally advanced NSCLC [13], to our knowledge, it has not been evaluated as a predictive biomarker in this setting. Therefore, our aim is to determine the predictive and prognostic significance of the evolving value of NLR in patients diagnosed with stage III NSCLC treated with definitive CRT.

Materials and methods

Patients

A single-center, retrospective study was conducted including patients diagnosed with inoperable stage III NSCLC and treated with concurrent or sequential CRT at Hospital Universitario Doctor Peset between 2010 and 2015. The patients were classified according to the guidelines of the tumor-node-metastasis (TNM) staging system of the Union for International Cancer Control (7th Edition) [14]. Patients older than 18 years old with histopathological diagnosis of NSCLC stage III that received treatment with radiotherapy and at least one cycle of chemotherapy were included. Patients were also excluded if their clinical or laboratory information was not available, if they had been diagnosed with another tumor during the previous 3 months or if an infection or an acute complication was found at the moment of the acquisition of the blood tests, since it could interfere with our results.

The clinicopathologic characteristics, comorbidities, and laboratory data were recorded and archived at the hospital informatics system. Complete blood cell counts with differential count were collected at baseline (before receiving any treatment) and 5–6 weeks after completing CRT. This interval from the end of treatment and the blood test extraction enables us to avoid the possible myelotoxicity produced mainly by chemotherapy. Patients were also grouped according to their age: young patients (less than 70 years) vs. old patients (70 years or older). The cut-off point was set at 70 years old, because it is the age at which the majority of age-related changes start to happen and this population should be taken into special consideration regarding treatment options and possible toxicities [15].

Response criteria were defined according to the guidelines of response evaluation criteria in solid tumors (RECIST, v.1.1 [16]) with a CT scan of the chest and upper abdomen. Adverse events were evaluated by common terminology criteria in adverse events (CTCAE) v.4.0. Patients were followed every 3 months for the first 2 years, every 6 months for 3 years, and then every year or until death.

The study was conducted in accordance with the Declaration of Helsinki and after obtaining approval of the institutional research ethical committee. Informed consent was exempted due to the retrospective nature of the study and assured anonymity.

Statistical analysis

NLR is defined as the absolute neutrophil count divided by the absolute lymphocyte count [10] and it was evaluated before receiving any treatment and 5–6 weeks after completing CRT. NLR was considered a continuous variable and was also dichotomized as low vs. high using the cut-off point described in the previous studies and meta-analyses (cut-off value = 4) [17]. NLR monitoring preceding and following CRT stratified two groups: good (NLR remained < 4 and NLR decreased ≥ 4 to < 4) and poor prognostic group (NLR increased from < 4 to ≥ 4 and NLR remained ≥ 4).

Odds ratios (OR) were calculated using multivariate models for binary outcome. Specifically, a multivariate logistic regression model was applied to evaluate response to therapy, measured by RECIST and categorized into two groups: progressive disease and responsive disease (including complete response, partial response, and stable disease). The predictors in the model were the type of treatment (sequential or concurrent CRT), type of chemotherapy (Cisplatin doublet vs. Carboplatin doublet), ECOG-PS at diagnosis, age group, and NLR-based prognostic group. Considering that the NLR-based prognostic groups include parameters pre and post-treatment, it cannot be evaluated as a predictive

factor of response previous to therapy; however, its relationship with response to treatment can be assessed.

Progression-free survival (PFS) and overall survival (OS) were calculated from the start of treatment to radiographic or clinical progression and death, respectively; and were estimated with a multivariate Cox regression model including NLR, age group, ECOG-PS at baseline, type of treatment (concurrent vs. sequential CRT), and type of chemotherapy (cisplatin doublet vs. carboplatin doublet). Living patients were censored at the date of last follow-up. Significant predictors were further analyzed with Kaplan–Meier curves.

Statistical analyses were performed using the G-STAT software. All tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Patients and tumor characteristics

Ninety-two patients were included in the final analysis. The demographic and tumor characteristics are shown in Table 1. Patients ranged in age from 39 to 83 years (median age 65.5). Most patients were male (85.9%) and had a current or former history of the smoking habit (96.7%). The majority of patients presented with a good performance status (19.6% patients had ECOG 0; 70.6%, ECOG 1, and 9.8%, ECOG 2); and it did not change during treatment nor in the following weeks after finishing it. The predominant histology was squamous cell carcinoma (56.5%). Also, more than half of the patients were diagnosed with stage IIIB NSCLC (63.1%). Chemotherapy regimens administered were based in platinum doublets (carbo- or cisplatin plus paclitaxel, docetaxel, etoposide, or vinorelbine) and patients received at least 54 Gy of thoracic radiation therapy either concurrently or sequentially. Median pre-treatment NLR was 3.08 (range 1.00–0.88) and post-CRT was 4.29 (range 0.80–75.00).

At data cut-off (March 31st 2019), 64 patients had progressed (69.57%) and 60 patients had died (65.21%). Only three patients died because of toxicity of the treatment or comorbidities; in the rest of the cases, the cause of death was tumor progression.

Table 1 Demographics, clinical, and tumor characteristics of patients included ($n = 92$)

Age (years)	
Median (range)	65.5 (39– 82)
Young patients—No. (%)	62 (67.4%)
Older patients—No. (%)	30 (32.6%)
Sex—No. (%)	
Female	13 (14.1%)
Male	79 (85.9%)
Smoking status—No. (%)	
Non-smoker	3 (3.3%)
Ex-smoker	41(44.5%)
Current smoker	48(52.2%)
ECOG performance status score—No. (%)	
0	18 (19.6%)
1	65 (70.6%)
2	9 (9.8%)
Histology—No. (%)	
Adenocarcinoma	36 (39.1%)
Squamous carcinoma	52 (56.5%)
Other	4 (4.4%)
Clinical stage (TNM staging 7th edition)	
IIIA	34 (36.9%)
IIIB	58 (63.1%)
Type of CRT scheme—No. (%)	
Concurrent	71 (71.2%)
Sequential	21 (22.8%)
Type of chemotherapy—No. (%)	
Cisplatin-based	22 (23.9%)
Carboplatin-based	70 (76.1%)
Pre-treatment NLR	
Median (range)	3.08 (1.00–10.88)
Post-treatment NLR	
Median (range)	4.29 (0.80–75.00)
Prognostic groups—No. (%)	
Good prognosis (NLR decreases < 4 or remains < 4)	42 (45.6%)
Poor prognosis (NLR increases ≥ 4 or remains ≥ 4)	50 (54.4%)

Impact of treatment received

To assess whether the type of treatment (sequential vs. concurrent CRT) had an influence on response to therapy, we used a multivariate logistic regression model including also ECOG-PS at diagnosis, age groups (young vs. old), type of chemotherapy (cisplatin doublet vs. carboplatin doublet), and prognostic groups based on NLR dynamic values. Response to treatment was evaluated by RECIST measures in CT scan performed 5–6 weeks after finishing CRT. Patients were divided into two groups depending on their best response to therapy: progressive disease vs. responsive disease (including patients with complete response, partial response, and stable disease). As shown in Table 2, type of treatment regarding the sequence of chemotherapy and radiotherapy did not influence our results. Accordingly, the type of treatment did not impact progression-free survival nor overall survival (data shown in Table 3).

Table 2 Odds ratios (ORs) for the best response to treatment (responsive disease vs. progressive disease) using a multivariate logistic regression model

Variable	Odds ratio (CI 95%)	*p* value
ECOG	2.63 (0.71–9.79)	0.147
Age group (young vs. old, cut-off point = 70 years)	1.36 (0.25–7.57)	0.719
Type of treatment (concurrent vs. sequential)	1.18 (0.17–7.88)	0.862
Type of chemotherapy (Cisplatin doublet vs. Carboplatin doublet)	1.36 (0.22–8.25)	0.735
Prognostic groups (good vs. poor)	4.94 (1.01–24.48)	0.048

Table 3 Univariate analysis and multivariate Cox regression model evaluating the impact on progression-free survival and overall survival of ECOG, age group, type of treatment, and prognostic groups according to dynamics of NLR

Progression-free survival				Overall survival			
Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Hazard ratio (CI 95%)	*p* value	Adjusted hazard ratio (CI 95%)	*p* value	Hazard ratio (CI 95%)	*p* value	Adjusted hazard ratio (CI 95%)	*p* value
ECOG							
1.43 (0.94–2.18)	0.090	1.65 (1.05–2.60)	0.030	1.52 (0.98–2.36)	0.063	2.02 (1.26–3.25)	0.003
Age group (young vs. old, cut-off point = 70 years)							
1.02 (0.62–1.68)	0.938	1.44 (0.76–2.71)	0.263	1.08 (0.65–1.83)	0.750	1.58 (0.81–3.07)	0.180
Type of treatment (concurrent vs. sequential)							
0.91 (0.50–1.65)	0.755	0.50 (0.23–1.08)	0.078	0.94 (0.50–1.77)	0.849	0.49 (0.21–1.12)	0.090
Type of chemotherapy (cisplatin doublet vs. carboplatin doublet)							
1.35 (0.58–1.84)	0.906	1.27 (0.64–2.53)	0.494	1.19 (0.66–2.16)	0.562	1.71 (0.82–3.55)	0.152
Prognostic groups (good vs. poor)							
2.83 (1.67–4.80)	< 0.001	2.98 (1.74–5.10)	< 0.001	2.63 (1.52–4.53)	< 0.001	2.81 (1.62–4.90)	< 0.001

Response to treatment: relationship with dynamics of NLR

Our multivariate analysis revealed that the only factor independently associated with response to treatment was the prognostic group depending on behavior of NLR during treatment. Patients with NLR increasing to ≥ 4 or remaining ≥ 4 after CRT (poor prognosis group) had a higher risk of achieving a progressive disease as the best response to treatment [Odds ratio 4.94 (CI 95 % = 1.01–24.48); *p* value = 0.048]. In addition, the disease control rate was 95.24% in the good prognosis group vs. 80% in the poor prognosis group, although this trend was not statistically significant (Fisher's exact test, double-sided *p* value = 0.057). On the other hand, ECOG-PS, age, and type and sequence of treatment did not have any impact on treatment response.

Survival outcomes: prognostic value of dynamics of NLR

Univariate analysis and multivariate Cox hazard model were used to determine whether ECOG-PS, age, type of treatment, type of chemotherapy, and NLR-based prognostic groups were associated with PFS and OS (data shown in Table 3). ECOG was shown as an independent prognostic factor for survival, and PFS and OS were shorter in patients with poor ECOG. Prognostic groups considering dynamics of NLR after treatment were also related to PFS and OS on our multivariate analysis. PFS was 25.79 months for the good prognosis group and 12.09 for the poor prognosis group [HR 2.98 (CI 95% = 1.74–5.10], $p < 0.001$); and OS was 42.94 months and 18.86 months, respectively [HR 2.81 (CI 95% = 1.62–4.90), $p < 0.001$]. Survival curves were estimated using the Kaplan–Meier method and the log-rank test (data shown in Figs. 1 and 2). Therefore, NLR-based groups after CRT are shown to be prognostic factors in our study.

Discussion

The immune system holds a crucial part in cancer development, because it takes part in the tumoral surveillance, but it can also induce an inflammatory state and promote its growth [18, 19]. As cancer-associated inflammation is one of the hallmarks of cancer, and plays an important role in tumor development and progression, it is crucial to have information about the immunological and inflammatory status of the host.

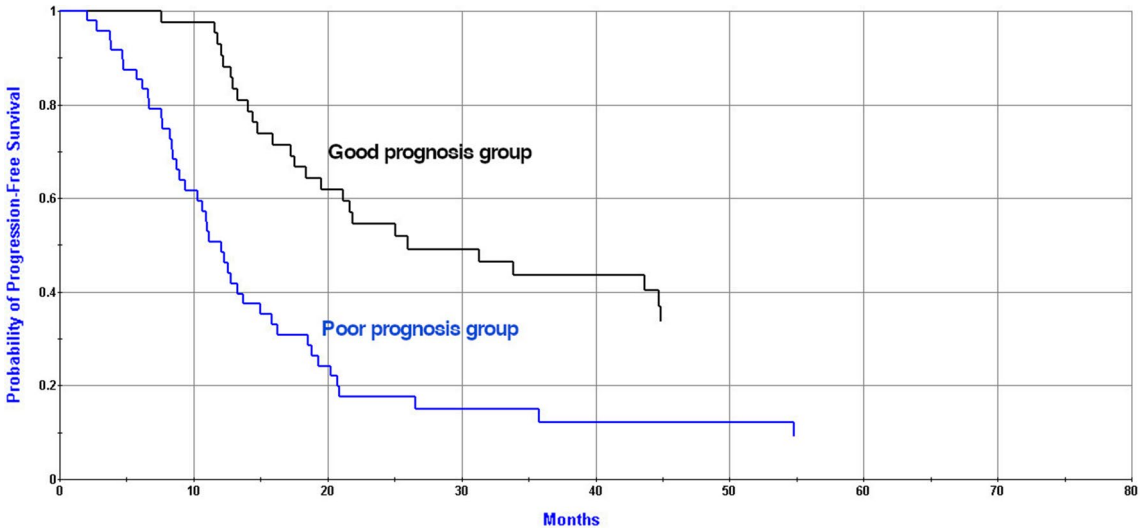

Fig. 1 Kaplan–Meier curves for progression-free survival (PFS) in the good vs. poor prognostic groups

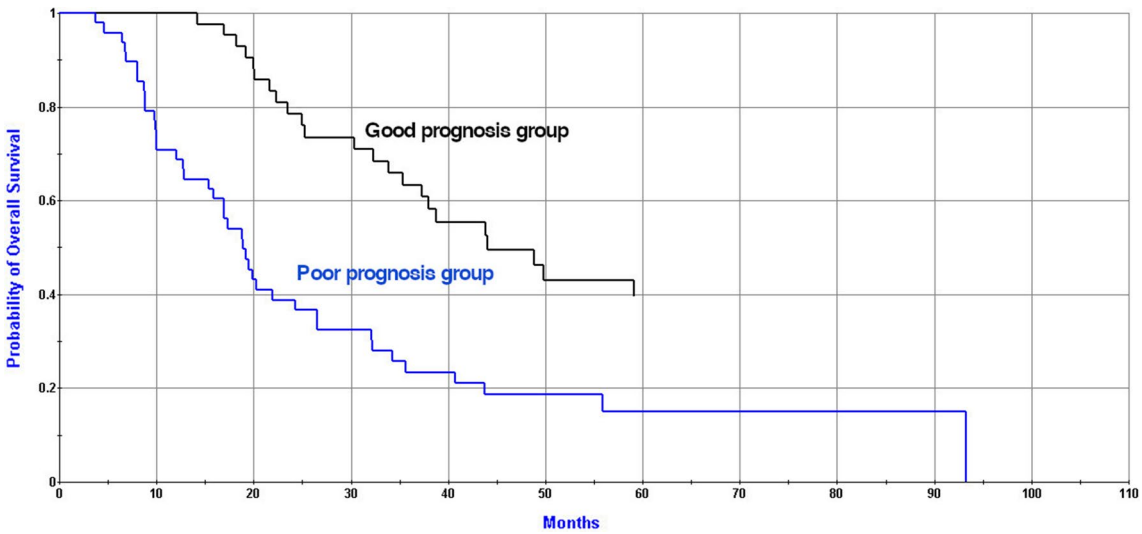

Fig. 2 Kaplan–Meier curves for overall survival (OS) in the good vs. poor prognostic groups

These factors can be evaluated with markers from peripheral blood samples that are inexpensive and easily reproducible. One of the most widely studied inflammatory-based scores is the neutrophil-to-lymphocyte ratio. Baseline NLR has been demonstrated to be a prognostic factor for PFS and OS in different cancer types [20, 21], and particularly in NSCLC given its relationship with inflammation. Neutrophils and lymphocytes are suggested to play an essential role in tumor development: neutrophils produce pro-inflammatory cytokines that inhibit the cytolytic activity of other immune cells and lead to cancer initiation and progression; on the contrary, lymphocytes are the most prominent anti-tumor cells (especially CD8 + T lymphocytes) [22]. Moreover, higher NLR, mainly related to neutrophilia and lymphopenia, may reflect the inflammatory status of the tumor microenvironment [23]. However, NLR is a dynamic marker that can be influenced not only by the host condition, but also by the treatment received and the response generated, and this has been studied to a lesser extent.

In our study, we demonstrated that variation of NLR at baseline and 5–6 weeks after completing multimodal treatment with chemoradiotherapy is useful to evaluate the systemic inflammatory status of patients and that it is related to response to treatment and survival. Specifically, a reduction of NLR was significantly associated with a better tumor response, achieving higher rates of disease control, and a

longer progression-free survival and overall survival regardless of treatment strategy (concurrent vs. sequential CRT or chemotherapy regimen) and age. ECOG was not associated with response to treatment; however, most of our patients had a Performance Status of 0–1, and that is why, they were considered suitable for multimodal treatment. Conversely, poor ECOG was significantly related to a shorter PFS and OS.

The impact of baseline NLR in response to chemotherapy in advanced NSCLC was reported previously by Yao et al. [24], and subsequently, high NLR was also associated with a poorer response to targeted therapy [8] and immunotherapy [12, 25, 26], including the evaluation of variation of NLR during treatment. Nevertheless, there are scarce data in stage III NSCLC, and only evaluating pre-treatment NLR [27]. In this study by Tang et al., CRT was combined with an antiangiogenic therapy (recombinant human endostatin) which is not used in clinical practice and could have interfered with their results. Other inflammation-related biomarkers such as the Glasgow prognostic score and the systemic inflammation index have been studied as predictive factors in locally advanced NSCLC [28, 29], supporting the impact of the inflammatory and immunological host condition in response to multimodal treatment in stage III NSCLC.

The role of NLR as a prognostic factor for PFS and OS in our study was consistent with the previous publications [30, 31], showing that a higher NLR is related to a worse prognosis. Furthermore, our results highlight the importance of the dynamics of NLR, demonstrating that post-treatment inflammatory status is a better predictor of PFS and OS than baseline NLR. Previously, lower lymphocyte nadir value during radiation therapy for stage I–III NSCLC was associated with poorer survival [32]. These findings suggest that a reduction in the inflammatory response associated with the tumor might be presented as a reduction of NLR, and that is why, it is crucial to understand the dynamic evolution of NLR during and after treatment.

On one hand, the limitations of our study include its retrospective nature, which hinders the complete exclusion of concurrent inflammatory conditions especially after finishing CRT; the single institution basis; and the relatively low sample size. Furthermore, the NLR threshold is not yet standardized. Based on the previous studies and meta-analysis, we used four as the cut-off point [33]; nevertheless, it has been suggested that the prognostic role of inflammatory indexes may be influenced by the TNM stage [34], and their prognostic yield might vary among different stages and tumors and should be determined in prospective studies.

On the other hand, the strong points of our study should also be outlined: to our knowledge, this is the first published study evaluating the dynamics of NLR in locally advanced NSCLC treated with chemoradiotherapy in a non-Asiatic population. Our population includes patients receiving exclusive CRT using platinum doublets, whereas other studies focused on stage III NSCLC also included patients in which surgery was performed [13, 28], making our population more homogeneous. Furthermore, our study emphasizes the importance of blood-based biomarkers not only as prognostic elements, but also correlating them with response to treatment. With the great development of drugs that enhance the immune system to fight against tumors, it is essential to find biomarkers that can easily be applied in clinical practice and that might be deeply investigated to help clinicians to elucidate which patients might benefit from consolidation treatment with immunotherapy and which patients may have a higher risk of toxicity, especially in the locally advanced setting, in which oncologists try to maximize their efforts to offer patients the most suitable treatment.

As the interaction between the host and the tumor, also influenced by treatment, may produce changes in the immunological and inflammatory condition, and considering the importance of our findings, we believe that blood biomarkers such as NLR should be prospectively studied in randomized clinical trials.

Conclusions

In conclusion, our study demonstrates that variation in NLR after CRT in stage III NSCLC correlates with tumor response, PFS, and OS regardless of treatment strategy and age. A high post-CRT NLR is significantly associated with poor survival outcomes in patients with stage III NSCLC undergoing radical treatment. Therefore, NLR could be used as a surrogate marker evaluating the efficacy of treatment and prognosis in this population. Furthermore, NLR should be evaluated as a predictive factor in patients receiving immunotherapy after CRT.

That is why, NLR, with a demonstrated prognostic value, should be taken into account in the design of clinical trials as we believe that it could be useful in treatment decision-making and patient selection for consolidation treatment with immunotherapy or subsequent therapy lines.

Acknowledgements The authors would like to express our gratitude to Joanna Gołąb for her contribution providing language help for the manuscript.

Author contributions VP-A: designed the research, acquired the data, and contributed to the data analysis and interpretation. He also prepared the first draft of the manuscript edited and reviewed it. TS-C: designed the research, and helped with the data analysis and the preparation of the first draft of the manuscript. Moreover, she reviewed it and edited the final version. STC: participated in the design of the statistical analysis and also performed it. Besides this, she reviewed the manuscript and edited the final version. VGB: participated in the design of the statistical analysis and also performed it. Besides this, he reviewed the manuscript. MMU: helped with the study design, the

data acquisition, and interpretation, and also reviewed the manuscript. IC MM: also conducted the study design, helped with the data interpretation, and edited the final version of the manuscript. All authors approved the final version of the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Code availability IRB number 25/17.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and it was approved by the Ethics Committee of Hospital Univeristario Doctor Peset (IRB number 24/17). The manuscript has not been published and is not under consideration for publication elsewhere.

Research involving human participants and/or animals The study was conducted in accordance with the Declaration of Helsinki and after obtaining approval of the institutional research ethical committee.

Informed consent Informed consent was exempted due to the retrospective nature of the study and assured anonymity.

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