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Review Article

Lung cancer tumor markers in serous effusions and other body fluids

Jaume Trapé[a,b,c,1,*], Silvia Bérgamo[a,b,d,1], Laura González-Garcia[a,b] and Carolina González-Fernández[a,e]

[a]*Department of Laboratory Medicine, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Catalonia, Spain*
[b]*Tissue Repair and Regeneration Laboratory, Centre for Health and Social Care Research, University of Vic – Central University of Catalonia, Vic, Catalonia, Spain*
[c]*Faculty of Medicine, University of Vic – Central University of Catalonia, Vic, Catalonia, Spain*
[d]*Doctoral School, University of Vic – Central University of Catalonia, Vic, Catalonia, Spain*
[e]*Gastrointestinal Oncology, Endoscopy and Surgery Research Group, Manresa, Catalonia, Spain*

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Abstract. From its onset and during its progression, lung cancer may affect various extrapulmonary structures. These include the serous membranes, the pleura and pericardium, and less frequently the central nervous system, with leptomeningeal involvement. In these cases, fluid accumulates in the serous membranes which may contain substances secreted by the tumor. Measuring the concentrations of these substances can provide useful information for elucidating the origin of the fluid accumulation, either in pleural and pericardial effusions or in cerebrospinal fluid. This paper describes the histological types of lung cancer that most frequently affect the serosa and leptomeninges. It also reviews the literature on tumor markers in different fluids and makes recommendations for their interpretation.

Keywords: Lung cancer, tumor markers, effusions, review, recommendations

1. Introduction

Lung cancer (LC) is the third most common cancer in the United States. According to the American Cancer Society, 236,740 new cases are expected in the general population in 2022, with an estimated mortality rate of 130,180 cases [1]. In 2020, there were more than 2.2 million new cases of LC worldwide with a forecast of 1.8 million deaths.

In Europe the data are similar to those of the US. In 2020, 2,339,617 cases of lung cancer were recorded, representing 13.5% of tumors among men (315,054 cases) and 7.9% among women (162,480 cases) [2]. Lung cancer is the leading cause of death due to cancer in men and the third highest in women [3]. It rose from fourth to third place among women in 2019, probably due to the increase in tobacco consumption in women since 1970 [4].

[1]Silvia Bérgamo and Jaume Trapé have contributed equally to this paper.

*Corresponding author: Jaume Trapé PhD, Laboratory Medicine, Althaia Xarxa Assistencial Universit`ria de Manresa, Dr Joan Soler 1-3, 08243 Manresa, Catalonia, Spain. E-mail: jtrape@althaia.cat.

The severity of the prognosis of LC means that the clinical practices for the treatment of the disease need to be continuously updated. Today, due to advances in the understanding of specific molecular pathways, it is possible (and also essential) to differentiate between adenocarcinoma, squamous cell carcinoma, and other histological types of LC. Thanks to this new knowledge, targeted therapies can be designed which incorporate drugs that are effective against particular types of tumor but may be toxic in other contexts (for example, tyrosine kinase inhibitors).

The 2015 World Health Organization (WHO) classification reflects the distinction between types of LC [5].

1.1. Non-small cell lung cancer

- Adenocarcinoma

Currently this is the most common histological type. Like squamous cell carcinomas, adenocarcinomas are made up of large cells [6]. The nuclei are vesicular and clear, with nucleoli; the cytoplasm is wide, with formation of vacuoles of mucus. Adenomas present great heterogeneity, and often have more than one morphological pattern within the same tumor [7].

- Squamous cell carcinoma

Histologically, these tumors are made up of large cells and abundant cytoplasm. Well-differentiated forms present keratinization of the cytoplasm and intercellular bridges. From the immunohistochemical perspective, they express high molecular weight cytokeratins and CEA [8].

- Large cell carcinoma

The morphology, architecture and immunohistochemistry of these large lung cancer cells differ from those of the other histological types (i.e., squamous, glandular or small cell lung cancer, SCLC).

1.2. Neuroendocrine tumors and SCLC

These tumors express neuroendocrine markers (chromogranin, synaptophysin and CD5). Prognosis is poor, and EGFR mutations have occasionally been described.

- Adenosquamous carcinoma
- Sarcomatoid carcinoma
- Unclassifiable carcinomas and others

A frequent complication of lung cancer is pleural and/or pericardial effusion and, to a lesser extent, leptomeningeal involvement. Very often, the pleural effusion is the first sign patients notice and is the reason why they consult their doctor.

Approximately 20% of patients with lung cancer develop a pleural effusion at some point in their disease, and between 2% and 7% have pericardial effusion [9]. Although brain metastases are common, fewer than 1% have leptomeningeal involvement [10, 11].

The rates of serous effusions are not the same in all types of LC. They are more frequent in adenocarcinomas; due to their peripheral location and ability to metastasize, they more easily invade the pleura and pericardium, creating malignant effusions as the first sign of cancer. In squamous cell carcinoma, pleural effusions occur more frequently once the disease is progressing. For their part, SCLCs are particularly aggressive and present a high proportion of effusions and a high level of leptomeningeal involvement, though less than adenocarcinoma. Table 1 shows neoplasms associated with malignant pleural effusions.

Table 1
Pathologies associated with malignant pleural effusions [39]

Malignancy	Histologic subtype	Prevalence (%)
Lung cancer	Adenocarcinoma (ADC)	29–37
	Small Cell Lung Cancer (SCLC)	6–9
	Squamous cell carcinoma (SCC)	2
Breast cancer	Breast adenocarcinoma	8–40
Gynecological malignancy	Ovarian adenocarcinoma	18–20
Gastrointestinal cancer	Gastric adenocarcinoma	2
	Colorectal adenocarcinoma	1
	Pancreatic adenocarcinoma	3
Kidney Cancer	Renal Cell Carcinoma	1
Hematological malignancy	Lymphoma	3–16
Skin cancer	Melanoma	5–6
Mesothelioma	Malignant mesothelioma	1–6
Sarcoma	Sarcoma	1–3

2. Lung cancer and effusions

An effusion is a pathological accumulation of fluid in the space between the visceral and parietal serosa (the pleural or pericardial space). In cancer patients there are two main types:

– Neoplastic or malignant effusions, in which the serosa is colonized by tumor cells; in most cases they are exudates.
– Paraneoplastic or paramalignant effusions, in which, in general, the serosa is not colonized by tumor cells. Strictly speaking, these include only effusions in cancer patients that cannot be attributed to specific processes (e.g., cardiogenic shock, cirrhosis, etc.). They can be either transudative or exudative, [9, 12]. The Table 2 shows type and etiology of serous effusions in patients with lung cancer according to Light's criteria.

Table 2
Type and etiology of serous effusions in patients with lung cancer

Transudates	Exudates
Paraneoplastic	Neoplastic or malignant
• Obstruction of lymph vessel	• Neoplastic invasion of serosa
• Pulmonary thromboembolism	• Mesothelioma
• Hypoalbuminemia	• Infiltration due to contiguity
• Superior vena cava syndrome	• Metastasis
• Atelectasia	Paraneoplastic
• Radiotherapy	• Pulmonary thromboembolism
• Chemotherapy (cardiotoxicity)	• Pulmonary obstruction with pneumonia
	• Radiotherapy
	• Chemotherapy (toxicity in serosa)
	• Opportunistic infections (pericardial effusions)

Effusions in LC may have different etiologies:

- Malignant, with infiltration of the serosa by tumor cells: direct involvement of the membrane due to infiltration by contiguity or metastasis, and secretion of cytokines such as vascular endothelial growth factor.
- Disruption of the thoracic duct: metastasis, infiltration.
- Reduced lymphatic drainage: metastasis.
- Increased hydrostatic pressure: superior vena cava syndrome.
- Reduced oncotic pressure which can occur with cachexia, massive liver metastases and the resulting hypoalbuminemia.
- Decreased pleural pressure: atelectasis or trapped lung.
- Direct damage to the serosa due to ionizing radiation or chemotherapy (alectinid).
- Heart failure caused by chemotherapy.
- Increase in pulmonary interstitial fluid: pulmonary thromboembolism, and pneumonia due to tumoral bronchial obstruction or secondary to treatment.

3. Diagnosis of neoplastic effusions

It is important to correctly diagnose pleural fluids as malignant or non-malignant according to the TNM classification of the International Association for the Study of Lung Cancer (IASLC) (8th edition, 2015) [13]. The presence of malignant pleural or pericardial effusion is associated with low patient survival. Patients with stage I/III lung cancer and benign serous effusions (pleural and/or pericardial) are candidates for tumor resection, and have a better prognosis than patients with malignant effusion even with the same TNM; the latter are considered metastatic (M1a), and are non-operable [14].

Therefore, an accurate differential diagnosis in these patients is essential in order to establish prognosis and select treatment. The simplest definitive method for diagnosing a neoplastic effusion is pleural fluid cytology. Between 30% and 50% of cytologies are negative, and percutaneous pleural biopsy increases the sensitivity for detecting malignant pleural effusion by 10%. Thoracoscopy has additional diagnostic value in undiagnosed cases of exudative pleural effusion with high clinical suspicion of malignancy, but it is a highly invasive procedure. Therefore, alternative methods are necessary to be able to select patients for these tests.

4. Tumor markers and effusions

4.1. Pleural effusion

Tumor markers (TMs) play a key role in the differential diagnosis of serous effusions. It is difficult to establish reference limits for TMs in this context, since the measurement is only performed in cases of an accumulation of fluid due to a pathological cause; fluid is not extracted in healthy individuals.

Tumor markers are used for differential diagnosis in effusions with etiologies other than cancer, for example infectious, immunological, and chemical etiologies in which the mesothelium is compromised, and others involving physical processes such as decreased colloid osmotic pressure or increased hydrostatic pressure that do not affect the integrity of the mesothelium. Two types of TM are found in effusions [15]:

1. TMs that are not usually secreted by the mesothelium in benign conditions (e.g., CEA, CA15-3, CA72-4, CA19-9); concentrations are lower in the fluid than in serum.

2. TMs that are normally secreted by mesothelial cells in benign conditions [16] (CYFRA 21-1, CA125, and mesothelin) at concentrations higher than those described in serum in healthy individuals and with a fluid/serum ratio greater than 1 : 1.

Metastases are among the most frequent causes of malignant pleural effusion; they mainly affect the lung, breast, ovaries and the lymph system [17].

Several authors have studied TMs in serous fluids to distinguish between benign and malignant conditions, usually without taking into account the capacity of the mesothelium to produce them. The results obtained vary widely, so it is difficult to recommend a cut-off value and determine the diagnostic yield. The Barcelona consensus of 1994 proposed the following steps [18]:

- Assess marker concentration
- Rule out false positives
- Control evolution

In this situation, it is difficult to control evolution since in most cases only one measurement is available, and in the rest of the cases the time between the samples is insufficient for adequate interpretation. In addition, it should be borne in mind that there are many variables that can affect TM concentrations, such as the analytical technique used, the cut-off value chosen, the presence of benign diseases that can increase TM concentrations such as tuberculosis, empyemas, or inflammatory processes caused by other conditions [19].

For TM assessment to be useful, high specificity is necessary and the number of false positives must be reduced. This is achieved by raising the cut-off point of the TMs to ensure that benign pleural effusions do not exceed it. As Table 3 shows, the studies with the highest discriminant values are the ones with the highest specificity. To improve sensitivity, the combined use of several TMs has been proposed [20].

5. Inflammatory processes and tumor markers: False positives

Some benign processes with high levels of inflammation or necrosis of the serosa and surrounding tissues, such as empyema and tuberculous or complicated parapneumonic effusions, can present high TM concentrations in serous fluid. The levels may reach up to 10 times the concentrations of benign effusions without inflammation.

Excluding purulent effusions, Porcel et al. (2017) obtained a slight improvement in sensitivity [41% (45 ng/mL) vs 31% (50 ng/mL) for CEA and 40% (77 IU/mL) vs 37% (75 IU/mL) for CA15-3] with cut-off points similar to or slightly lower than when these effusions are included [21].

These inflammatory effusions are easily identifiable using routine laboratory biomarkers such as adenosine deaminase (for tuberculous effusions or empyema), differential leukocyte count (for empyema or complicated parapneumonic effusions) or C-reactive protein as a marker of inflammation (for tuberculous effusions, empyema, parapneumonic effusions, and severe inflammation) [22, 23], which we can term markers of benignity. These tests allow us to identify false positives and to apply higher discriminant values in patients with positive biomarkers of benignity, thus improving the specificity.

Another cause of high values of TMs in serous fluids is the passage from serum to fluid through the membrane, either due to the presence of tumors that do not invade the mesothelium or other pathological processes such as kidney failure or liver disease that raise serum TM concentrations [22]. These possible false positives can be detected by the fluid/serum (F/S) ratio [24]. Patients with neoplastic invasion of the mesothelium will present higher concentrations in fluid than in serum, while

Table 3
Diagnostic value of tumor markers in pleural effusions

Tumor marker	Cut-off point	Sensitivity	Specificity	Units	Author	Assay
CEA	45	41	100	ng/mL	Porcel et al. [21]	ECLIA
CA15-3	77	40	100	kU/L		
CEA	60	37	100	μg/L	Trapé et al. [40]	ECLIA
CA15-3	80	38	100	kU/L		
CA19.9	201	22	100	kU/L		
CA72.4	21	33	100	kU/L		
CEA	5.88	52	95	ng/mL	Santoribio et al. [41]	ECLIA
CA15-3	24.7	54	90	U/mL		
CA19.9	7.0	50	93	U/mL		
CA125	1433	33	95	U/mL		
CEA	2.0	65	95	ng/mL	Topolcan et al. [42]	TRACE
CA15-3	7.6	96	95	kIU/L		LIA
CA19.9	17.9	46	95	kIU/L		IRMA
CA125	2545	41	95	kIU/L		
CEA	2.2	56	89	μg/mL	Volaric et al. [43]	ECLIA
CA125	844.2	49	67	mU/mL		
CEA	2.9	84	97	ng/mL	Feng et al. [44]	ECLIA
CA19.9	12.89	60	92	U/mL		
Cyfra 21.1	43.1	67	86	μg/mL		
CEA	6.5	45	100	ng/mL	Gaspar el at. [24]	MPEIA
CA15.3	62.4	40	100	kU/L		
CA19.9	103	18	100	kU/L		
CEA	40	35	100	ng/mL	Villena et al. [45]	RIA
CA 15.3	53	40	100	IU/mL		
CA72.4	16	30	100	IU/mL		
Cyfra 21.1	150	24	100	U/L	Ferrer et al. [46]	RIA
CEA	40	35	100	ng/mL		
CA 125	1000	37	100	ng/mL		
CEA	288	24	100	ng/mL	Trapé et al. [47]	ECLIA
CA 125	2385	33	100	U/mL		
CA 15.3	82.2	54	100	U/mL		
CYFRA 21.1	175	50	100	ng/mL		
CA19.9	585.4	47	100	kU/L		
CEA	50	31	100	ng/mL	Porcel et al. [12]	ECLIA
CA 125	2800	19	100	U/mL		
CA 15.3	75	37	100	U/mL		
CYFRA 21.1	175	25	100	ng/mL		

ECLIA: Electrochemiluminescence immunoassay; MPEIA: Magnetic Particle Enzyme Immunoassay; TRACE: Time resolved amplified cryptate; LIA: Lumino-immune assay; IRMA: Immuno-radiometric assay; RIA: Radioimmunoassays.

in patients with elevated concentrations in serum the F/S ratio for markers that are usually produced by the mesothelium will be below 1 : 1.

Applying these criteria, our group has evaluated two strategies: one based on a high cut-off value (CEA = 60 μg/L, CA15-3 = 80 KU/L; CA19-9 = 201 KU/L and CA72-4 21 KU/L) and the other on a low cut-off point and F/S ratio (CEA = 5 μg/mL; CA15-3 = 30 KU/L, CA19-9 = 37 KU/L and CA72-4 = 6.7 KU/L and F/S>1.2), seeking maximum specificity [16]. The sensitivity and specificity of more

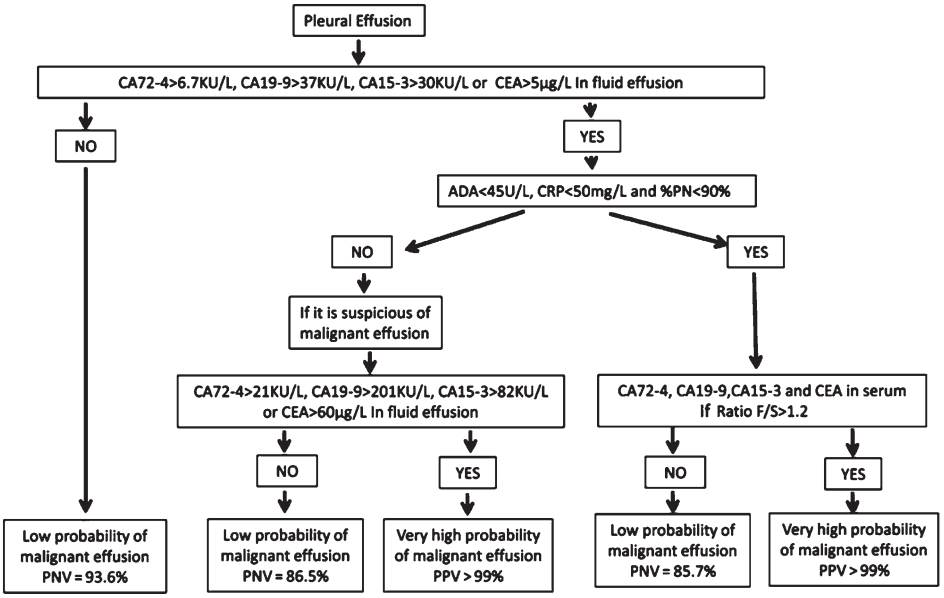

Fig. 1. Algorithm for interpretation of TMs in serous fluids [40].

than 400 pleural effusion samples were assessed, obtaining a sensitivity of 64% for the high cut-off point and 77% for the low cut-off point and F/S ratio, with specificities of 100% and 98% respectively.

When classifying them according to the biomarkers of benignity (ADA, CRP and % of polynuclear cells) in the group with negative values, the low cut-off point and F/S ratio strategy showed a sensitivity of 80% and a specificity of 100%, and for the high cut-off point the sensitivity was 67% at maximum specificity. In both strategies, the positive predictive value (PPV) was above 99%. For the group with positive biomarkers of benignity, the sensitivity fell in both strategies; maximum specificity was maintained in the high cut-off point strategy, but fell below 95% for the low cut-off point and F/S ratio, with a PPV of 68.8%.

To facilitate the interpretation of TMs in serous fluids, Figure 1 describes an algorithm based on the experience with pleural effusions. The cut-off points established for specificities of 100% in different studies by the same group may be different, so the PPVs may not reach 100%. For this reason, the PPVs are shown as greater than 99%.

6. Pericardial effusion

Very few studies have assessed tumor markers in pericardial fluid [22]. Szturmowicz et al. found higher concentrations of CEA and CYFRA 21.1 in malignant pericardial effusions than in non-malignant ones, obtaining values of 80 ng/mL and 0.5 ng/mL respectively for CEA and 260 ng/mL and 22.4 ng/mL for CYFRA 21.1. In view of their results, they proposed optimal cut-off values for these TMs of 5 ng/mL for CEA and 100 ng/mL for CYFRA 21.1 [23].

In previous work the same authors studied non-specific enolase (NSE), obtaining values of 41.8 ng/mL. They argued against its evaluation in blood samples [25].

Karatolios et al. also found higher values in malignant pericardial effusions with specificities of 100% for the following TMs:

[cut off (sensitivity) CEA, 8.5 ng/mL (48%), CA 19.9, 856(15%), CA 72.4, 19.5 UI/mL (45%); SCC, 216 ng/mL (4%), NSE, 348.5 ng/mL (7%)] [26].

Table 4
Diagnostic value of tumor markers in CSF with leptomeningeal involvement

Tumor marker	CSF concentration	Sensitivity	Specificity	Units	Author assay
CEA	4.522	81	100	ng/mL	Shi et al. [37] ELISA
CA125	1.720	93	65	U/mL	
CA15-3	1.695	61	93	U/mL	
CA19.9	1.47	69	79	U/mL	
CYFRA 21.1	1.51	79	90	ng/mL	
NSE	9.155	92	52	ng/mL	
CEA	0.279	97	100	ng/mL	Zhang et al. [36] CLIA
CYFRA 21.1	1.145	97	100	ng/mL	
CEA	3.4	71	88	ng/ml	Wang et al. [32] ECLIA
CYFRA 21.1	5.5	35	100	ng/ml	
NSE	14.6	57	67	ng/ml	
CYFRA 21.1	1.61	80	95	ng/mL	Hyun et al. [48] ECLIA

ELISA: double antibody sandwich enzyme linked immunosorbent assay; CLIA: immunochemiluminescent assay; ECLIA: electrochemiluminescence immunoassay.

The European Society of Cardiology guidelines [27] recommend cut-off points of 5 ng/mL for CEA and 100 ng/mL for CYFRA 21.1.

7. Cerebrospinal fluid

Approximately 20% of patients with lung cancer may have metastatic involvement of the central nervous system, although a few of them, around 10% [28], have leptomeningeal involvement, that is neoplastic meningitis (NM). Glass et al. reported that patients with brain metastases without leptomeningeal involvement did not present tumor cells in CSF [29]. The most frequent histological types in NM are SCLC and adenocarcinoma. Other tumors that can produce meningeal metastases are breast tumors, melanomas, lymphomas and leukemias [30, 31]. The diagnosis is made by CSF cytology, but the sensitivity is only 40–60% [32, 33].

Some TMs in cerebrospinal fluid have been studied as aids to diagnosis. As in the case of serous effusions, the discriminant values vary notably from study to study. In general, the CSF concentrations of non-neoplastic meningitis for most TMs (CEA, CA15-3, CA19-9, CA125 and CA72-4) are undetectable, while CSF concentrations of other markers such as NSE and S100 are low and indicate damage to the CNS [34, 35], and so false positives are possible. Table 4 displays the TMs and the discriminant values proposed by various authors.

In addition, increases in CSF TM concentrations due to leakage and/or dysfunction of the blood-brain barrier, or contamination via the blood due to traumatic lumbar puncture, may not have been correctly assessed [36, 37]. Therefore the intrathecal synthesis of the TMs should be measured, in the same way as other macromolecules such as specific IgG in infectious diseases or light chains in multiple sclerosis [31, 36]. Zhang et al. used cut-off points of 1.145 ng/mL for CYFRA 21-1 and 0.279 ng/mL for CEA, finding higher sensitivities and specificities than using the F/S ratio. For their part, Corsini et al. determined CEA, CA125, CA15-3 and CA19-9 in CSF and serum and also the intrathecal synthesis of TMs [38]. The sensitivity of intrathecal synthesis was 94.4% for CEA, 50% for CA125, 83.3% for CA15 -3 and 66.7% for CA19-9. Patients with NM presented intrathecal synthesis of at least one of these markers, but none of the patients with non-neoplastic neurological diseases showed intrathecal

synthesis of any TMs; therefore, this strategy seems more useful to be able to identify the origin of the malignant meningitis.

8. Conclusions

Lung cancer patients may present serous effusions due to different etiologies, either cancer- or non-cancer-related.

In lung cancer, invasion of the pleural and pericardial serosa by tumor cells is a frequent event. This invasion is more common in adenocarcinomas and SCLC than in other histological types.

Determining whether or not the effusion is malignant is important, given the implications for therapy. An error can lead to overtreatment (surgery when the effusion is malignant and is considered benign) or undertreatment (no surgery when it is benign and considered malignant), which can lead to a worse prognosis.

In the differential diagnosis of serous effusions, the cut-off points described for each of the TMs vary widely. The diagnostic performance of TMs is good when high cut-off points are used to obtain specificities greater than 99%, and combinations of TMs are used to increase sensitivity.

The diagnostic yield can be improved by identifying possible false positives and using specific cut-off points for each group, obtaining higher sensitivity for specificities above 99%.

Leptomeningeal metastases can occur during the progression of lung cancer, with ADC and SCLC being the most frequently involved tumors.

In non-neoplastic neurological processes, the concentrations of some TMs are usually undetectable. For correct interpretation, it is important to confirm the integrity of the blood-brain barrier and bear in mind its possible contamination due to traumatic lumbar puncture. The determination of the intrathecal synthesis of the markers may be a good alternative.

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Author contributions

CONCEPTION: JT and SB
DATA CURATION: SB, LG-G, CG-F and JT
ANALYSIS OF DATA: SB, LG-G. CG-F and JT
PREPARATION OF THE MANUSCRIPT: SB, JT and LG-G
REVISION FOR IMPORTANT INTELLECTUAL CONTENT: SB, LG-G, CG-F and JT
SUPERVISION: JT

Conflict of interest

Jaume Trapé, Silvia Bérgamo, Laura González-García and Carolina González-Fernández have no conflict of interest to report.

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