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Time to sputum conversion in patients with pulmonary tuberculosis: A score to estimate the infectious period

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ABSTRACT

Introduction: Patients with pulmonary tuberculosis (PTB) disease and positive sputum cultures are the main source of infection. Culture conversion time is inconsistent and defining the length of respiratory isolation is challenging. The objective of this study is to develop a score to predict the length of isolation period.

Methods: A retrospective study was carried out to evaluated risk factors associated with persistent positive sputum cultures after 4 weeks of treatment in 229 patients with PTB. A multivariable logistic regression model was used to determinate predictors for positive culture and a scoring system was created based on the coefficients of the final model.

Results: Sputum culture was persistently positive in 40.6%. Fever at consultation (1.87, 95% CI:1.02–3.41), smoking (2.44, 95% CI:1.36–4.37), >2 affected lung lobes (1.95, 95% CI:1.08–3.54), and neutrophil-to-lymphocyte ratio > 3.5 (2.22, 95% CI:1.24–3.99), were significantly associated with delayed culture conversion. Therefore, we assembled a severity score that achieved an area under the curve of 0.71 (95% CI:0.64–0.78).

Conclusions: In patients with smear positive PTB, a score with clinical, radiological and analytical parameters can be used as a supplemental tool to assist clinical decisions in isolation period.

1. Introduction

Pulmonary Tuberculosis (PTB) is an airborne disease considered a major global health problem. According to the World Health Organization, 10 million people developed tuberculosis, and 1.3 million people died from the disease in 2019 [1]. Despite the incidence rate and progressive decline in recent years (a 20% reduction between 2015 and 2020), eradication remains elusive.

Patients with PTB discharge infected droplet nuclei into the air that can infect healthy people. Once diagnosed, early respiratory isolation

Abbreviations: PTB, Pulmonary Tuberculosis; COPD, Chronic Obstructive Pulmonary Disease; DOT, Directly Observed Therapy; NLR, Neutrophil-to-lymphocyte Ratio; ROC, Receiver Operating Characteristic; OR, Odds Ratio; AUC, Area Under the Curve; DM, Diabetes Mellitus; PTBSCore, Pulmonary Tuberculosis Sputum-Conversion score.

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measures should be established to prevent transmission ideally until negative sputum culture samples are obtained. However, *Mycobacterium tuberculosis* has a slow growth in cultures, and the results are available 4–6 weeks after collection; nonetheless, clinicians have to decide whether to continue or remove isolation before knowing the culture results and based on the sputum smear results.

The objective of this study is to determine the risk factors related to the persistence of positive sputum cultures 4 weeks after treatment onset and to create a score that can predict the respiratory isolation time for each patient individually.

2. Methods

2.1. Study design, setting and participants

This multicenter retrospective observational study was performed at the Tuberculosis Units of 3 tertiary University Hospitals of Catalonia, Spain, namely, Arnau de Vilanova (Lleida), Vall d'Hebron (Barcelona), and Bellvitge (L'Hospitalet de Llobregat). Patients with smear-positive PTB were recruited. The inclusion criteria were (i) age $\geq$ 18 years old; (ii) positive acid-fast bacilli smear before treatment onset; (iii) sputum culture sample at 4 weeks after treatment onset. Subjects with HIV, with atypical mycobacteria infection, or lost to follow-up were excluded. The participants at Arnau de Vilanova University Hospital were evaluated from 1 January 2010 to 31 December 2017, whereas the participants at Vall d'Hebron and Bellvitge Hospital were evaluated from 1 January 2010 to December 2014.

2.2. Data collection

All cases of sputum smear-positive PTB obtained from the notifiable diseases registry in the study period were identified, and the medical records were reviewed retrospectively. The following data were obtained by medical chart review: demographic data (age, sex, and country of birth), alcohol abuse (alcohol intake exceeding 70 g per day), drug and tobacco use, comorbidities (cancer, immunosuppression, chronic liver disease, chronic renal failure, diabetes mellitus, and chronic obstructive pulmonary disease (COPD)). Patients were also assessed for clinical symptoms (fever, cough, hemoptysis, chest pain, expectoration, and weight loss) at diagnosis. Directly observed therapy (DOT), treatment tolerance, and hepatic toxicity were also recorded. The treatment adherence was evaluated using a urine colorimetric test or a close follow-up.

The pretreatment chest X-ray for each patient was reviewed and interpreted by an experienced radiologist. The presence or absence of cavities, pleural effusion, miliary pattern, and number of affected lobes were noted, and a radiological index that estimates the spread of the disease (proportion of total lung affected (%) + 40 if cavitation was present) was calculated [2].

In addition, laboratory data were collected including hemoglobin (g/dL), lymphocytes, leucocytes, neutrophils, and the neutrophil-to-lymphocyte ratio (NLR).

The results of the sputum smear obtained at diagnosis as well as the sputum culture sample collected 4 weeks after treatment onset were also recorded. The auramine stain was used during the study, and the bacillary load was measured by a semiquantitative method as numerous (one or more bacilli/oil immersion field), less numerous (10–99 bacilli/100 fields), and few bacilli (1–9 bacilli/100 fields) [3]. Cultures for *Mycobacterium tuberculosis* were carried out using the Lowenstein–Jensen technique or liquid culture, and antimicrobial susceptibility testing was performed.

For the outcome analysis, the persistence of infectivity was defined as a positive culture at 4 weeks after treatment start.

2.3. Statistical methods

Categorical variables were described as percentages, and continuous variables as median (interquartile range), as they did not follow a normal distribution (Kolmogorov–Smirnov test). For the comparison between the groups with positive (POSITIVE) or negative (NEGATIVE) cultures, the Mann–Whitney test was used for continuous variables and the chi square test for categorical variables. The significance level was $p < 0.05$.

The receiver operating characteristic (ROC) curve methodology was used to determine the optimal cutoff point for the NLR.

A multivariate logistic regression model was used to determine the independent predictors for a positive culture. All variables with a p value lower than 0.20 in the univariate analysis were entered into the multivariate model with a forward stepwise selection of variables. Odds ratios (OR) with their 95% confidence interval were calculated.

A simple score was developed based on the predictors that were independently associated with a positive culture in the multivariate analysis. The score points were defined according to the β coefficients by rounding to the next positive integer value. The sum of the points is the value of the final score. The discriminating property of the score was assessed using the area under the ROC curve (AUC with 95% CI). The calculations were performed using SPSS software, version 23.0 (SPSS, Chicago, Ill).

2.4. Ethics statement

The study protocol was approved by the Research Committee of each hospital.

3. Results

From 1 January 2010 to 31 December 2017, 619 patients were diagnosed with PTB in the three participant hospitals. Of these patients, 275 had one or more positive sputum smear tests (44.4%), and 229 fulfilled all the inclusion criteria. In total, 46 subjects were excluded from the outcome analysis: 8 were HIV positive, 7 had atypical mycobacteria, and 31 were lost to follow-up.

The patients included in the study had a median age of 43 (31–55) years, they were predominantly male (69%), and slightly more than half of them were active smokers (56%). The median interval between symptom onset and treatment start was 8 weeks (4–12). Cough (93%), purulent sputum (72%), and weight loss (68%) were the most common symptoms. The median interval between treatment start and sputum culture collection was 31 days (26–41). After the first month of treatment, 76 patients (33%) had a positive smear sputum compared with 93 (41%) with a positive culture. All patients firstly received standard treatment, and 7.9% were switched to alternative treatments due to resistance or intolerance. Two patients with a negative culture at 4 weeks discontinued treatment (one of them stopped treatment for 7 days at the first month for gastrointestinal intolerance and then reinitiated, the other one stopped treatment at the third month without affecting our study period). In total, 6.7% of the positive culture samples had isoniazid resistance and 0.4% were multidrug resistant. The baseline characteristics of the 229 patients studied are shown in Table 1, and the clinical and microbiological characteristics are detailed in Table 2.

The factors associated with a persistent positive culture after 4 weeks of treatment in the univariate analysis were smoking, alcohol abuse, cough, fever at consultation, weight loss, DOT, pleural effusion, high bacillary load, more than two affected lung lobes, the radiological index, and the NLR. The inclusion of an NLR higher than 3.5 was selected based on the most appropriate cutoff point on the ROC curve. The univariate analysis is detailed in Tables 1 and 2.

The multivariate analysis showed that smoking (OR, 2.44; 95% CI, 1.36–4.37), fever at consultation (OR, 1.87; 95% CI, 1.02–3.41), more than two affected lung lobes (OR, 1.95; 95% CI, 1.08–3.54), and an NLR

Table 1
Baseline characteristics associated with positive culture after 4 weeks of treatment. (N = 229).

	ALL N = 229	NEGATIVE N = 136	POSITIVE N = 93	*p*
Age (years)[a]	41 (31–55)	39 (30–53)	43 (33–56)	*0.174*
Age groups				*0.251*
< 30	24.5	25.0	23.7	
30–40	24.5	28.7	18.3	
41–55	29.3	27.2	32.3	
> 55	21.8	19.1	25.8	
Gender – (male)	68.6	64.0	75.3	*0.071*
Country of origin				*0.478*
Western Europe	57.2	56.6	58.1	
Eastern Europe	12.2	11	14	
Asia	1.3	1.5	1.1	
North Africa	9.2	11.8	5.4	
Rest of Africa	7	5.1	9.7	
South America	10.5	11	9.7	
Central America	0.4	0	1.1	
Arab countries	1.3	1.5	1.1	
Comorbidities				
Immunosuppression	3.1	2.2	4.3	*0.366*
COPD	8.5	5.9	12.9	*0.065*
DM	9.6	8.1	11.8	*0.346*
Cancer	7.0	8.8	4.3	*0.187*
Renal failure	2.6	2.9	2.2	*0.713*
Smoking	55.5	46.3	68.8	*0.001*
Alcohol abuse	20.5	15.4	28.0	*0.021*
Drug abuse	7.0	7.4	6.5	*0.793*

Values are presented as percentage. ([a]): mean ± standard deviation. ([b]): median (interquartile range). (p) calculated with chi-square test or Mann-Whitney test. Abbreviations COPD, Chronic obstructive pulmonary disease DM, diabetes mellitus.

of > 3.5 (OR, 2.22; 95% CI, 1.24–3.99) were significantly and independently associated with a persistent positive culture at 4 weeks after treatment onset (Table 3).

Based on these results, and in order to facilitate clinical use, we elaborated a scoring model to predict the culture positivity at 4 weeks, referred to as the PTBSCore, with scores ranging from 0 to 4 points (Fig. 1). Patients who scored four points had a high probability (82%) of having a persistent positive culture after 4 weeks of treatment. On the other hand, patients with zero or one point had a probability between 75 and 87% of having a negative culture. For the remaining patients, with two or three points, the probabilities were intermediate (36 and 51%, respectively). An ROC curve analysis was performed, and the novel PTBScore achieved an AUC of 0.71 (95% CI 0.64–0.78), indicating an appropriate discrimination of patients with a higher risk (Fig. 2).

4. Discussion

In clinical practice, it is very difficult to know when a patient with a positive smear sputum stops spreading the disease and being contagious; therefore, the end of the isolation period may be difficult to determine. On the one hand, a prolonged isolation period may be not necessary and could affect labor and family life. On the other hand, a short isolation period when a patient is still contagious could facilitate community transmission threating the goal of achieving eradication. It is crucial to recognize the end of the period during which the smear positive PTB patients are infectious; however, *M. tuberculosis* has a slow growth in cultures, and the auramine stain can be negatively correlated with the culture results.

To predict infectivity in patients with PTB, prior research has been reported without fully resolving the issue. *Horita* et al. developed an "Infectivity Conversion Score" classifying each patient according to the sputum smear grade and assessing the existence of cavitations in the lungs [4], and *Bisognin* et al. found that older age, high Xpert MTB/RIF result category, high smear grading, and severe involvement of the lung on radiography were risk factors for persistent sputum smear positivity [5]. Moreover, others have related an age of > 40 years, smoking, alcohol abuse, and diabetes mellitus with delayed sputum smear or culture conversion [5–10]. However, these studies were restricted to a reduced number of potentially predictive parameters and did not analyze the epidemiological, clinical, and biological parameters altogether. In addition, most of them did not use the sputum culture as a

Table 2
Clinical characteristics at consultation, treatment tolerance, radiological and analytical characteristics associated with positive culture after 4 weeks of treatment (N = 229).

	ALL N = 229	NEGATIVE N = 136	POSITIVE N = 93	*p*
CLINICAL SYMPTOMS				
Cough	93.4	90.4	97.8	*0.026*
Fever	62.0	55.9	71.0	*0.021*
Expectoration	71.6	67.6	77.4	*0.107*
Chest pain	27.9	27.9	28.0	*0.998*
Haemoptysis	19.4	19.3	19.6	*0.954*
Weight loss	67.7	61.0	77.4	*0.009*
Weeks *(a)	8 (4–12)	8 (4–14)	8 (4–12)	*0.256*
MICROBIOLOGY				
Pre-treatment smear grading				*0.033*
Negative	14.4	19.9	6.5	
Few	15.7	16.2	15.1	
Less numerous	43.2	40.4	47.3	
Numerous	26.6	23.5	31.2	
Resistance				*0.460*
Isoniazid	6.7	6.7	6.7	
Rifampicin	1.3	1.5	1.1	
Multidrug	0.4	0.7	0	
TREATMENT				
Anti-tuberculosis drug				*0.170*
Standard treatment	92.1	90.4	94.6	
Other	7.9	9.6	5.4	
DOT	19.2	14.7	25.8	*0.036*
Vomits**	11.9	11.2	12.9	*0.696*
Hepatic toxicity**	2.6	3.0	2.2	*0.700*
RADIOLOGY				
Cavitation	61.6	60.3	63.4	*0.631*
Alveolar pattern	84.1	81.3	87.9	*0.191*
Pleural effusion	16.6	12.5	22.6	*0.044*
Miliary pattern	18.8	16.9	21.5	*0.382*
Number of lobes				*0.005*
None	4.4	5.1	3.2	
1 lobe	34.5	41.2	24.7	
2 lobes	24.0	25.7	21.5	
> 2 lobes	37.1	27.9	50.5	
Radiological index[a]	60 (40–100)	60 (40–80)	80 (40–100)	*0.005*
BLOOD TEST[a]				
Haemoglobin	12.6 (11.3–13.7)	12.9 (11.4–13.7)	12.3 (11.1–13.7)	*0.185*
Leukocytes	8.9 (7.1–11.3)	8.5 (6.9–10.6)	10.1 (7.6–11.9)	*0.008*
Neutrophils	6.4 (4.7–8.4)	5.9 (4.4–7.5)	7.3 (5.0–9.4)	*0.001*
Lymphocytes	1.7 (1.1–2.2)	1.8 (1.3–2.3)	1.5 (0.9–2.0)	*0.020*
NLR	3.8 (2.6–5.9)	3.3 (2.4–5.2)	4.8 (3.1–7.3)	*<0.001*
NLR > 3.5	54.1	44.9	67.7	*0.001*

*weeks from onset of symptoms and initiation of treatment **Vomits and hepatotoxicity evaluated during first month of treatment.
Values are presented as percentage. ([a]) median (interquartile range (p) calculated with chi-square test or Mann-Whitney test.
Abbreviations: DOT, directed observed therapy. NLR, Neutrophil-to-lymphocyte ratio.

Table 3
Multivariate logistic regression analysis for risk factors of positive culture after 4 weeks of treatment.

Variable	B coefficient	OR (95 % CI)	p-value	Score points
Smoking	0.892	2.44 (1.36–4.37)	*0.003*	1
Fever at consultation	0.625	1.87 (1.02–3.41)	*0.042*	1
> 2 affected lobes	0.670	1.95 (1.08–3.54)	*0.027*	1
NLR > 3.5	0.798	2.22 (1.24–3.99)	*0.008*	1

Abbreviations: NLR, Neutrophil-to-Lymphocyte ratio; OR, Odds Ratio; CI, Confidence interval.

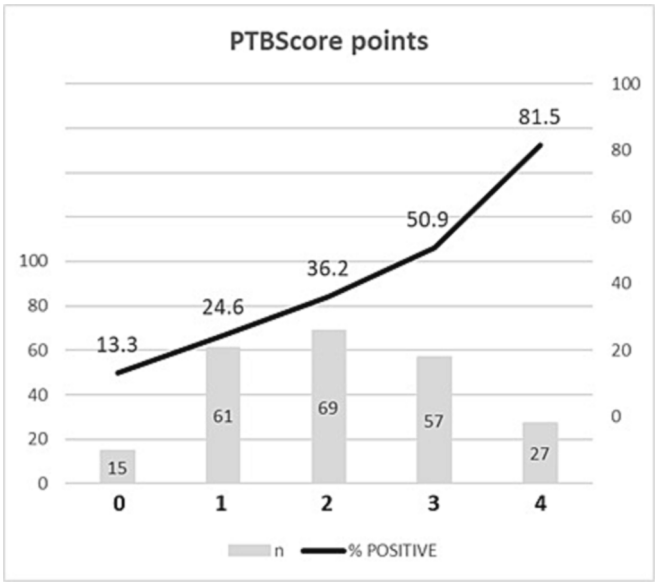

Fig 1. Percentage of positive cultures according to the number of risk factors. Abbreviations: PTBSCore, Pulmonary Tuberculosis Sputum-Conversion score.

reference, and they could be less reliable, as it was described by some investigators that a negative sputum smear due to the low presence of bacilli may remain contagious if the culture is positive [11–13], and on the other hand, a positive sputum smear with a negative culture may be due to the presence of nonviable organisms that are not able to grow in cultures, and the patient would not be contagious [14,15]. In our study, 17 patients presented with a negative smear and a positive culture at the first month of treatment, reinforcing the importance of this test instead of the smear to address infectivity.

Because of the poor scientific evidence, clinical guidelines cannot provide a clear recommendation about the isolation period, although some authors recognize a typical conversion period between 30 and 60 days [16,17]. Other guidelines suggest that respiratory isolation could be discontinued 2 to 3 weeks after the initiation of treatment if there is clinical improvement, low risk of resistance, and evidence of good therapeutic compliance [18–20], although these recommendations differ in several publications that have determined that approximately 40–60% of patients could be contagious after one month of initiating treatment [5,21,22]. These studies included patients with various nationalities (European, African, Asiatic, and Latin American) and comorbidities (HIV, DM, chronic bronchopathy, tobacco, and alcohol consumption), and in line with this data, in our investigation, 41% of patients remained culture positive at 4 weeks, a fact that supports the generalization of the score in subjects with different characteristics.

The immune response could be weakened by cigarette smoking,

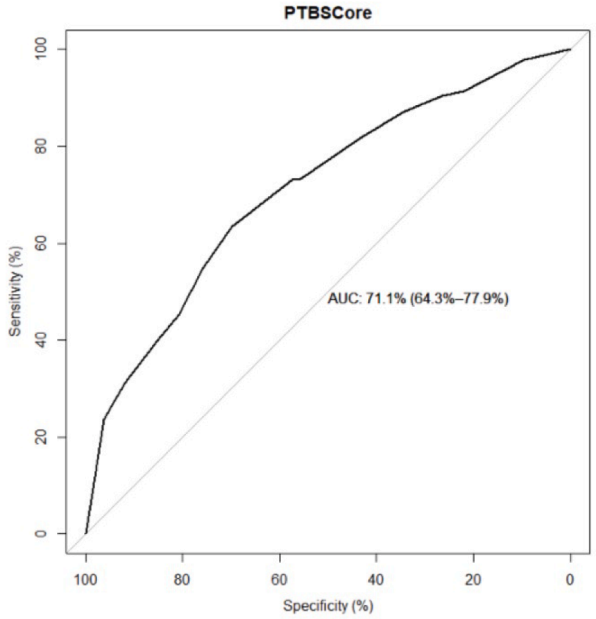

Fig 2. Regression model ROC curve. Abbreviations: PTBSCore, Pulmonary Tuberculosis Sputum-Conversion score; AUC, area under the receiver operating characteristic curve.

alcohol abuse, and other diseases such as diabetes mellitus, and this could be a reason for a delayed conversion. According to our results, smoking and alcohol abuse were statically associated with the persistence of infectivity, but no underlying disease was correlated with that finding, including diabetes mellitus or immunosuppression.

Clinical variables have usually been omitted in the majority of the studies; in our cohort, three clinical parameters at consultation, fever, cough, and weight loss were related to a longer duration of infectiousness. We hypothesize that fever may be related to a higher inflammatory response due to the presence of a high bacillary load at presentation. *Hatsuda* et al. found that nutritional markers predicted the delay of the conversion of sputum cultures to negative, and this could be due to the altered immune system responses against TB caused by malnutrition [23]. The significant association with cough had less value because of the high percentage of patients that presented with this symptom.

Our cohort included patients from developed and developing countries, with varying sociodemographic backgrounds and living standards. This design suggests similar trends might be occurring in heterogeneous settings and clinical contexts. We decided to exclude HIV-infected patients from the study because the number of patients was small and may not be representative. Furthermore, *Telzak* et al. and *Domínguez-Castellano* et al. have demonstrated that HIV status does not prolong the time to culture conversion [24,25]. Therefore, the PTBSCore cannot be used in HIV-positive patients and needs further validation.

Our results also found that lymphopenia and the NLR were strongly associated with delayed culture conversion. This pattern was similar to that described by *Chedid* et al., who reported that lymphopenia had a significantly longer time to sputum culture conversion at two months of treatment and hypothesized that patients with high baseline blood white cell counts and low lymphocyte proportions had highly inflammatory clinical patterns [26]. An increased NLR was related to the prognosis and mortality of PTB [27]. Based on our experience, a high NLR may also be useful in relation to a slower culture conversion, and this is the first study describing the association.

We evaluated several radiological findings detecting an association between the radiological index and the number of affected lung lobes with persistence in culture positivity in the univariate analysis. In the

literature, radiographic features were associated with smear non-conversion, especially the extent of the pulmonary involvement and the presence of cavitations [7,25,28,29]. *Ralph* et al. developed a radiologic index concluding that the presence of cavities and percentage of affected lung area were related to the severity of PTB [2]. These findings could be due to the high bacillary load in the necrotic material in consolidations or cavities that drain bacilli to the central airways.

Finally, related to the microbiological results, we found an association between a high bacillary load in the sputum smear and the time to sputum culture conversion, as widely described [6,7,24,28]. In addition, it is reasonable to believe that the presence of multidrug resistant strains of *M. tuberculosis* could be related to the persistence of positive cultures as reported by *Fortun* et al. [21]; however, resistance in our area is extremely low, and we could not study this association in our sample.

Among these parameters statistically associated with the persistence of the infectivity in the univariate analysis, four were selected in the multivariate analysis: smoking habit, fever at the consultation, more than two affected lung lobes, and an NLR higher than 3.5. These variables allowed us to perform a score named the PTBSCore, with four parameters that are commonly measured at consultation and can be easily tested in order to extend the isolation period when a high risk of transmission is estimated. The ROC curve analysis showed an AUC of 0.71 indicating a useful discrimination for our model. If such potential risk factors are known at the start of treatment, subjects can be stratified before the commencement of therapy: Patients with 0–1 point have a low probability of being infectious at 4 weeks after treatment start, those who score 2–3 points have an intermediate risk, and subjects with 4 points have a high risk of being contagious. This stratification may improve TB control and may offer greater efficiency in resource utilization. For example, patient with 4 points could be isolated for 8 weeks instead of 4 to prevent transmission, patients with 0–1 point could have 4 weeks of isolation, and patients with an intermediate risk (2–3 points) could wait to end quarantine until the negative culture results are obtained.

Our study had several limitations. First, several patients from one of the participant centers with a PTB diagnosis that fulfilled the inclusion criteria, could not be selected in the initial analysis (excluded from 619 subjects) because of data heterogeneity (clinical parameters were not clearly specified in medical record, some analytical variables were not available and subsequent follow up was irregular). Second, patients with HIV were not evaluated, and we could not extrapolate the results in this group of patients. Third, we are aware that sputum positivity is not the sole criteria for infectivity, but other parameters that can indicate contagiousness such as no clinical improvement, bad tolerance, and adherence to treatment are less objective variables, not always well described in medical records, and difficult to predict. Finally, for further investigation, an external validation and a prospective study are needed to determine the prediction model's reproducibility and generalizability to new and different patients with a cohort of similar characteristics to address the accuracy of the PTBSCore.

In summary, we developed a score with four easy-to-use parameters that predicts a persistent positive culture and therefore contagiousness in patients with PTB 4 weeks after treatment onset. If validated, it could be very useful in clinical practice to determine the isolation time and prevent further spreading.

CRediT authorship contribution statement

Maria Ramirez-Hidalgo: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Javier Trujillano-Cabello:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. **Adrià Espluges-Vidal:** Conceptualization, Writing – review & editing. **Mercé Reñé-Reñé:** Writing – review & editing. **Miguel Santín:** Conceptualization, Investigation, Resources, Writing – review & editing. **Adrián Sánchez-Montalvá:** Investigation, Resources, Writing – review & editing. **Albert Bernet-Sánchez:** Resources, Writing – review & editing. **Laura Gros-Navés:** Writing – original draft, Writing – review & editing. **Miquel Falguera:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

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