Usefulness of infection biomarkers for diagnosing bacteremia in patients with a sepsis code in the emergency department

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SUMMARY

The objective of this study was to assess the usefulness of the biomarkers lactate, C-reactive protein (CPR) and procalcitonin for the diagnosis of bacteremia in patients with suspected sepsis in the emergency department (ED) and according to the focus of infection. We conducted a retrospective study among patients included in the sepsis code of our ED between November 2013 and December 2017. We analyzed demographic variables, co-morbidity according to the Charlson Index and focus of infection, blood cultures and classification according to Gram staining. We determined the diagnostic performance of the biomarkers quantitatively and calculated the area under the curve (AUC) for global bacteremia and as a function of the focus of infection. We included 653 patients with a median age of 79 years (interquartile range: 66-86), of whom 287 (44.0%) were women. The most frequent infectious focus was respiratory (36.1%]. Blood cultures were requested in 87.5% (569 cases). Of the tested samples, 31.3% were positive, of which 63.5% revealed Gram-negative (GN) bacteria. Procalcitonin obtained globally the best AUC 0.70 (95% CI: 0.65-0.75). The values with the best sensitivity and specificity were 2.54 ng/mL for procalcitonin, 4.1 mmol/L for lactate and 156 mg/L for CRP. We found an association between the median procalcitonin value and GN bacteria (6.02; IQR: 1.39-39.40) and Gram-positive bacteria (1.74; IQR: 0.22-15.61). Procalcitonin is the biomarker with the greatest capacity to diagnose bacteremia, particularly in GN infection. Stratification by focus is important since not all biomarkers discriminate in the same way.

Keywords: bacteremia, sepsis, emergency department.

INTRODUCTION

Sepsis is a clinical entity that upholds a front-line position in the emergency department [ED] [1]. The current definition of sepsis focuses on the organic dysfunction caused by a pathogenic microorganism present in the organism [2]. Central to improving the survival of these patients is the early clinical diagnosis and the rapid implementation of a series of measures, which have now been protocolized in different international consensuses [3, 4].

Recent years have seen the development of the use of different biomarkers of infection that can help in decision-making and serve as both diagnostic and prognostic tools [5, 6]. Regarding the prediction of bacteremia, a biomarker should be

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able to identify in the ED the probability of bacteremia in the patient, as well as its etiology, favoring the initiation of early and adequate antimicrobial treatment [7-9]. Although there are many biomarkers of inflammatory response, the three that have demonstrated significant clinical relevance and are readily available in routine clinical practice are serum lactate, C-reactive protein (CRP) and procalcitonin (PCT) [10-13]. The usefulness of these biomarkers has been established in critical or pediatric patients. However, few studies assess their usefulness in the ED [14, 15].

In this context, our study aimed at assessing the usefulness of biomarkers (lactate, CRP and PCT) for the diagnosis of bacteremia in patients with suspected sepsis in the ED according to the focus of infection.

PATIENTS AND METHODS

Study design

We conducted a retrospective study in patients above 14 years of age included in the code sepsis (CS) of the ED of the University Hospital "Río Hortega" of the city of Valladolid (Spain) from November 2013 to December 2017. This project has clearance from the clinical research ethics committee of the center where the study was developed.

Patients selection

Patients are included in the CS and were therefore eligible to participate in the study if they had a suspected infection and also fulfilled 2 or more of the following criteria: heart rate >90 bpm, respiratory rate >20, O_2 saturation <90%, temperature >38.5ºC or <36ºC, alteration of the usual level of consciousness or signs of poor perfusion, mean arterial pressure <65 mmHg or systolic blood pressure <90 mmHg, leukocytosis >12000 mm^3 or leukopenia <4000 mm^3, lactate >2 mmol/L, PCT >2 ng/mL, parameters of organic dysfunction of one or more organs (platelets <100000/mm3, bilirubin >2 mg/dL in the absence of known liver disease, creatinine >1.5 mg/dL in the absence of known renal failure, international normalized ratio [INR] >1.5 or activated partial thromboplastin time >60 seconds in the absence of anticoagulant therapy). As of June 2016, patients were included in the CS if they had a suspected infection and a qSOFA score ≥ 2 points.

Definition and collection of variables

We reviewed the clinical records of the included patients for the following variables: blood cultures, presence of microorganisms [in case of positivity, microorganisms were classified as Gram-negative (GN) or Gram-positive (GP) or mixed bacteria]. A blood culture was considered positive when it was reported as such by the microbiology service in one of the samples. The independent variables were: age, gender and as clinical variables, comorbidity using the Charlson index (low-medium or high), focus of infection (respiratory, urinary, abdominal, indeterminate, others) and the following biomarkers: lactate (mmol/L), CRP (mg/dL) and PCT (ng/dL).

Statistical analysis

All data were stored and analyzed in XLSTAT® BioMED for Microsoft Excel® [version 14.4.0.] and Statistical Product and Service Solutions (SPSS, version 20.0) databases. We carried out a descriptive study of the samples. Continuous quantitative variables are described as median and interquartile range (IQR). The qualitative variables are described by absolute and relative frequencies (%). For the comparison of means of quantitative variables, the Student's t test was used with normally distributed values and the Mann-Whitney U test if there was no normal distribution. The chi-square test was used for 2x2 contingency tables and/or contrast of proportions to stipulate the association or dependence relationship between qualitative variables. In the tests performed, a confidence level of 95% was considered significant ($p<0.05$). The area under the curve (AUC) of the receiver operating characteristic (ROC) of each of the biomarkers analyzed (lactate, CRP and PCT) was calculated for the presence of positive blood cultures globally and for each of the foci of infection studied. We determined the cut-off points that offered greatest sensitivity and specificity for each biomarker and analyzed the ROC curves that reached statistical significance, calculating the positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Finally, each of the AUC obtained from all the scales was compared by means of non-parametric tests. In all the tests performed, a confidence level of 95% and a p value below 0.05 were considered significant.

RESULTS

A total of 653 patients were included in the study, of whom 287 were women (44.0%). The median age was 79 years (IQR 25-75: 66-86 years). In the comorbidity study, only 208 patients (32%) had a high Charlson comorbidity index. Of the total of the patients analyzed, 20 (3.1%) were diagnosed with non-infectious processes. Regarding the origin of the infection, the vast majority of patients were distributed between the respiratory (36.1%) and urological (30.2%) foci (Table 1). Blood cultures were requested from a total of 569 patients (87.1%), of whom 178 (31.3%) tested positive (Table 1).

In the case of urinary origin, 42.9% of the blood cultures tested positive, while in other foci of infection the positivity percentage decreased significantly (Table 2). Among the patients with bacteremia, the isolated microorganisms were pathogenic GN bacteria in 63.3% of the cases, whereas a mixed result was obtained in 2 cultures. Table 3 shows the distribution of GP and GN pathogens according to focus of infection, highlighting that GN pathogens were present in the majority of patients with bacteremia in both the urinary focus (90.5%), abdominal (73.7%) and in the indeterminate focus (63.6%); while the respiratory focus (75.6%) and other foci (100%) presented mostly GP pathogens ($p<0.0001$). The patients with positive blood cultures had a median age of 81 years (IQR: 69-87), whereas the median age of patients with negative blood cultures was 77 (IQR: 67-86) ($p<0.05$). All biomarkers presented significantly higher median values among patients with bacteremia compared to patients without bacteremia (Table 2).

All AUC of the biomarkers were found to reach statistical significance for predicting bacteremia in the overall sample as shown in Table 4. The biomarker that obtained the best AUC was PCT with a value of 0.70 (95% CI 0.65-0.75) followed by lactate with an AUC of 0.65 (95% CI 0.60-0.70) and CRP with a value of 0.57 (95% CI 0.52-0.63). When comparing biomarkers, we found no significant differences for CRP, neither with PCT ($p<0.001$) nor with lactate ($p<0.05$) (Table 5). The analytic values with highest sensitivity and joint specificity were 2,54 ng/mL for PCT, 4,1 mmol/L

Table 1 - Patient characteristics and association with requests for blood cultures.

	Total	*Blood culture not requested*	*Blood culture requested*	*P-value*
Number [n [%]]	653 [100]	84 [12.9]	569 [87.1]	
Sex				
Male [n [%]]	366 [56]	42 [11.5]	324 [88.5]	
Female [n [%]]	87 [44]	42 [14.6]	245 [85.4]	NS
Age [years [Median [IQR]]	79 [66-86]	79 [67-86]	79 [67-86]	NS
Charlson index [n [%]]				
Absence-low	442 [68]	51 [11.5]	391 [88.5]	
High	208 [32]	32 [15.4]	176 [84.6]	NS
Lactate [mmol/mL] [[Median [IQR]] [n]	2.55 [1.7-4.1] [624]	2.3 [1.57-4.62] [554]	2,6 [1.7-4] [70]	NS
CRP [mg/dL] [[Median [IQR]] [n]	111 [40.75-215] [634]	120,5 [45-234] [556]	111 [40-211] [78]	NS
PCT [ng/dL] [[Median [IQR]] [n]	1.3 [0.22-7.88] [497]	2.84 [0.37-23.52] [466]	1,27 [0.21-7.31] [31]	NS
Focus of infection [n [%]]				
Respiratory	236 [36.1]	27 [11.4]	209 [88.6]	
Urological	197 [30.2]	22 [11.2]	175 [88.8]	
Indeterminate	97 [14.9]	11 [11.3]	86 [88.7]	
Abdominal	69 [10.6]	12 [17.4]	57 [82.6]	
Other	34 [5.2]	6 [17.6]	28 [82.4]	
No infection	20 [3.1]	6 [30]	14 [70]	NS

n: number; %: percentage; IQR: interquartile range; CRP: C-reactive protein; PCT: procalcitonin, NS: not significant.

Table 2 - Characteristics of patients with blood cultures and confirmed focus of infection.

		Total	*BC+*	*BC-*	*P-value*
Number [n [%]]		569 [100]	178 [31.3]	391 [68.7]	
Sex					
	Male [n [%]]	324 [56.9]	101 [31.2]	223 [68.8]	
	Female [n [%]]	245 [43.1]	77 [31.4]	168 [68.6]	NS
Age [years] [Median [IQR]]		79 [66-86]	81 [69-87]	77 [67-86]	<0.05
Charlson index [n [%]]					
	Absence-low	391 [69]	119 [30.4]	272 [69.6]	
	High	176 [31]	58 [33]	118 [67]	NS
Lactate [mmol/mL] [[Median [IQR]] [n]		2.55 [1.7-4.10] [554]	3.2 [2.1-5.3] [175]	2.3 [1.58-4.63] [379]	<0.001
CRP [mg/dL] [[Median [IQR]] [n]		111 [40-215] [556]	139 [54-252] [172]	120 [45-234] [384]	0.003
PCT [ng/dL] [[Median [IQR]] [n]		1.3 [0.22-7.89] [466]	5,13 [0.78-26.4] [151]	2.84 [0.37-23.52] [315]	<0.001
Focus of infection [n [%]]					
	Respiratory	209 [36.7]	41 [19.6]	168 [80.4]	
	Urological	175 [30.8]	75 [42.9]	100 [57.1]	
	Indeterminate	86 [15.1]	34 [39.5]	52 [60.5]	
	Abdominal	57 [10]	19 [33.3]	38 [66.7]	
	Other	28 [4.9]	6 [21.4]	22 [78.6]	
	No infection	14 [2.5]	3 [21.4]	11 [78.6]	<0.001

BC+: positive blood culture; BC-: negative blood culture; n: number; %: percentage; IQR: interquartile range; CRP: C-reactive protein; PCT: procalcitonin, NS: not significant.

Table 3 - Characteristics of patients with positive blood culture according to Gram stain [excluding patients with mixed infections].

		Total	*GP*	*GN*	*P-value*
Number [n [%]]		176 [100]	61 [34.7]	115 [65.3]	
Sex					
	Male [n [%]]	99 [56.2]	31 [31.3]	68 [68.7]	
	Female [n [%]]	77 [43.8]	30 [39]	47 [61]	NS
Age [years] [Median [IQR]]		81 [69.25-87]	82 [71-87]	80 [67-87]	NS
Charlson index [n [%]]					
	Absence-low	119 [68]	39 [32.8]	80 [67.2]	
	High	56 [32]	22 [39.3]	34 [60.7]	NS
Lactate [mmol/mL] [[Median [IQR]] [n]		3,2 [2.05-5.35] [173]	3 [2-4.9] [59]	3.6 [2.1-5.6] [114]	NS
CRP [mg/dL] [[Median [IQR]] [n]		144,5 [53-253] [170]	127 [43-347] [59]	158 [54-238] [111]	NS
PCT [ng/dL] [[Median [IQR]] [n]		5.13 [0.79-26.5] [149]	1.74 [0.22-15.61] [50]	6.02 [1.39-39.42] [99]	<0.05
Focus of infection [n [%]]					
	Respiratory	41 [23.3]	31 [75.6]	10 [24.4]	
	Urological	74 [42]	7 [9.5]	67 [90.5]	
	Indeterminate	33 [18]	12 [36.4]	21 [63.6]	
	Abdominal	19 [10.8]	5 [26.3]	14 [73.7]	
	Other	6 [3.4]	6 [100]	0	
	No infection	3 [1.7]	0	3 [100]	<0.001

GN: Gram negative, GP: Gram positive; BC-: Blood culture negative; n: number; IQR: interquartile range; CRP: C-reactive protein; PCT: procalcitonin, NS: not significant.

Table 4 - Area under the curve of the different biomarkers, best cut-off points for greatest sensitivity and joint specificity, globally and according to focus of infection.

Focus	*AUC [95% CI]*	*p-value*	*Cut-off point*	*Se % [95% CI]*	*Sp % [95% CI]*	*PPV [95% CI]*	*NPV [95% CI]*	*LR [+] [95% CI]*	*LR [-] [95% CI]*
Global									
Lactate	0.654 [0.604-0.705]	<0.0001	4.1	40.6 [33.6-48.0]	80.26 [78.4-86.1]	51.8 [43.5-60.0]	75.1 [70.7-79.0]	2.33 [1.76-3.09]	0.72 [0.62-0.83]
CRP	0.579 [0.527-0.631]	<0.05	156	48.8 [41.5-56.3]	64.4 [59.7-69.2]	38.2 [32-44,8]	73.8 [68.9- 78.2]	1.38 [1.12-1.69]	0.79 [0.66-0.94]
PCT	0.705 [0.653-0.758]	<0.0001	2.54	60.3 [52.3-67.7]	70.5 [65.2-75.2]	49.5 [42.3-56.6]	78.7 [73.3-83.1]	2.04 [1.65-2.53]	0.56 [0.45-0.70]
Respiratory									
Lactate	0.652 [0.550-0.753]	0.003	2.6	66.7 [51.0-79.4]	62.7 [55-69.8]	30.2 [21.5- 40.6]	88.6 [81.5-93.2]	1.79 [1.33-2.41]	0.53 [0.33-0.85]
CRP	0.570 [0.468-0.672]	NS							
PCT	0.626 [0.518-0.733]	0.022	6.02	47.2 [32.0-63.0]	82.3 [74.8-87.9]	42.5 [28.5-57.8]	84.9 [77.6-90.1]	2.67 [1.61-4.43]	0.64 [0.46-0.90]
Urinary									
Lactate	0.671 [0.588-0.753]	<0.0001	2.8	63.5 [52.1-73.6]	64.9 [55-73.3]	58 [47.2-68.2]	70 [59.9-78.5]	1.81 [1.31-2.50]	0.56 [0.40-0.79]
CRP	0.537 [0.449-0.625]	NS							
PCT	0.718 [0.633-0.803]	<0.001	0.49	90.0 [80.5-95.5]	45.5 [35.5-55.8]	53.8 [44.3-63.1]	87 [74.3-93.9]	1.66 [1.35-2.04]	0.21 [0.10-0.47]
Indeterminate									
Lactate	0,609 [0,485-0,733]	NS							
CRP	0.706 [0.548-0.801]	0.001	107	72.2 [55.8-84.9]	60.8 [47.1- 73.0]	54.5 [40.1-68.3]	77.5 [62.5-87.7]	1.85 [1.24-2.77]	0.45 [0.24-0.82]
PCT	0.675 [0.548-0.801]	<0.001	0.97	80 [62.7-90.5]	47.8 [34.1- 61.9]	50 [36.4-36.4]	78.6 [60.5-89.8]	1.53 [1.10-2.13]	0.42 [0.19-0.91]
Abdominal									
Lactate	0.668 [0.513-0.823]	0.03	4.30	52.6 [31.7-72.7]	78.4 [62.8-88.6]	55.6 [33.7-75.4]	78.4 [62.8-88.6]	2.43 [1.15-5.14]	0.60 [0.35-1.03]
CRP	0.584 [0.423-0.744]	NS							
PCT	0.774 [0.627-0.992]	<0.0001	0.83	94.4 [74.2-99.0]	52 [33.5-70.0]	58.6 [40.7-74.5]	92.9 [68.5-98.7]	1.97 [1.29-3.00]	0.11 [0.02-0.74]
Others									
Lactate	0.619 [0.351-0.888]	NS							
CRP	0.559 [0.269-0.849]	NS							
PCT	0.833 [0.535-1]	0.02	0.95	66.7 [20.8-93.9]	88.9 [67.2-96.9]	50 [15.0-85.0]	94.1 [73-99]	6 [1.30-27.77]	0.38 [0.07-1.93]

AUC: Area under the curve, Se: Sensitivity, Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR [+]: Positive likehood ratio; LR [-]: Negative likehood ratio.

Table 5 - Comparison of the area under the curve [AUC] of the receiver operating characteristic [ROC] curves for the biomarkers according to the focus of infection.

		CRP	*PCT*
Global	Lactate	*0.033*	0.086
	CRP	1	*0.000*
Respiratory	Lactate	0.226	0.667
	CRP	1	0.358
Urinary	Lactate	*0.029*	0.364
	CRP	1	*0.000*
Indeterminate	Lactate	0.271	0.458
	CRP	1	0.609
Abdominal	Lactate	0.414	0.117
	CRP	1	*0.022*
Other	Lactate	0.791	0.122
	CRP	1	*0.000*

CRP: C-reactive protein; PCT: procalcitonin.

for lactate and 156 mg/L for CRP (Table 4).
When stratifying according to focus of infection, we observed that PCT presented a significant AUC in all, with results ranging from 0.62 (95% CI 0.51-0.73) for the respiratory focus to 0.83 (95% CI 0.535-1.0) in the group of other foci. Lactate presented a significant AUC in the respiratory focus (0.65; 95% CI 0.55-0.75), urinary (0.67; 95% CI 0.58-0.75) and abdominal (0.66; 95% CI 0.51-0.82), whereas CRP only obtained a significant AUC in the indeterminate focus (0.70; 95% CI 0.58-0.82) (Table 4).
The PCT value offering best joint sensitivity and specificity for the respiratory focus was 6.2 ng/dL. For the rest of the foci, these values were much smaller: 0.49 ng/dL for the urinary focus, 0.83 ng/dL for abdominal focus, 0.95 ng/dL for other foci and 0.97 ng/dL for the indeterminate focus. The lactate values found for the foci with a significant AUC were 2.6 mmol/L for the respiratory focus, 2.8 mmol/L for the urinary and 4.3 mmol/L for the abdominal focus (Table 4).
Next, we examined the relationship between the median values of the biomarkers and the presence of GN or GP bacteria in positive blood cultures. We found an association between the median of PCT and GN (6.02; IQR: 1.39-39.40) as well as GP bacteria (1.74; IQR: 0.22-15.61) ($p<0.05$), whereas this association disappeared with lactate and CRP (Table 3).

DISCUSSION

The present study analyzes the usefulness of different biomarkers for the diagnosis of bacteremia in patients treated with suspected sepsis in the ED. Our patients had an advanced age, although without high comorbidity, and were predominantly male. The vast majority had respiratory or urinary infections.
Blood samples were requested from most patients, and almost a third of all blood cultures were positive. This exceeds the number found in other similar studies, in which the bacteremia did not reach 13% [16]. This may be because in those studies the patients only had suspected infection, whereas our series included patients with a high suspicion of sepsis, explaining the higher number of positive results. Moreover, patients with bacteremia in our study were significantly older, which coincides with the susceptibility of the population over 65 years of age to develop both bacteremia and serious infections [17].
Among the different foci studied, the urinary focus showed the highest percentage of bacteremia; almost half of the patients with a request for a blood culture had bacteremia. The respiratory focus was the one with the lowest positivity. Two thirds of bacteria isolated from the blood cultures were GN, which were the main pathogens responsible for the infection of urinary and abdominal origin, while the bacteremia by GP bacteria was higher in the respiratory and indeterminate foci and those classified as other foci.
The mean values of PCT, lactate and CRP were significantly higher in those patients with positive blood cultures compared to those patients without bacteremia, which already indicates that bacteremia must be suspected in the presence of high values of any of these. However, not all have the same discriminative capacity; PCT was the biomarker that had the highest capacity to diagnose bacteremia among patients treated with the code sepsis. This biomarker offered the best AUC globally, much more so than CRP, which has a very limited diagnostic capacity. In the analysis by focus, we verified that the capacity of PCT to diagnose bacteremia is maintained in all the foci studied [18]. In addition to PCT, lactate was also superior to CRP in the global analysis, and it offered best results in the study of the respiratory focus but lost its diagnostic capacity in the

indeterminate focus and in other foci [19]. Of the three biomarkers analyzed, CPR performed worst overall, which confirms what was found by other authors and suggests that CPR is not a suitable biomarker for the diagnosis of bacteraemia in the emergency department [20]. However, we believe that this biomarker still has its usefulness, as our results indicate that in patients without a clear focus of infection, CPR obtains the highest diagnostic capacity of bacteraemia over PCT and lactic acid.

It is important to determine a cut-off value for each biomarker for assuming bacteremia among patients with suspected sepsis. In our work, the value with highest sensitivity and specificity for PCT was 2.54 ng/L, exceeding that of other studies that proposed a cut-off point with the highest specificity and sensitivity of 2-2.25 ng/mL [20, 21]. These differences can be attributed again to the fact that these works refer to globally infected patients and not to patients with suspected sepsis such as ours and that it seems that in these *a priori* more serious patients, the PCT levels to suggest bacteremia should be somewhat higher than what the scientific literature currently recommends. Similarly, the lactate value with highest sensitivity and joint specificity 4.1 mmol/L exceeded that of Kruse et al., where values above 2.5 mmol/L served as an independent predictor of severity, poor clinical evolution and mortality [22]. A study conducted by Green et al. found that adult patients treated in an ED with lactate values >4 mmol/L and CRP >10 mg/dL had a high risk of death (OR: 112.3; 95% CI: 6.8-22.3) [23].

In the analysis by infection focus, the value with best joint sensitivity and specificity of each biomarker varies significantly depending on the focus. Thus, in the case of PCT, it is remarkable that in the urinary focus this value does not reach 0.50 ng/dL while in respiratory infections it exceeds 6 ng/dL. Supposedly, to suspect bacteremia, we must find higher PCT values in the respiratory focus than in the other foci. Similarly, with lactate values around 2.5 mmol/L and an abdominal, respiratory or urinary focus, we can suspect bacteremia, while in the abdominal focus, this value necessarily exceeds 4.3 mmol/L.

Bacteremia was not associated with certain age groups, gender or comorbidity. However, in agreement with other studies, higher PCT values were observed in bacteremia due to GN infections. Perhaps this fact is owed to a more potent inflammatory response to GN bacteria than to GP bacteremia [24-26].

Clearly, our results support the use of the analyzed biomarkers as a complementary diagnostic tool for bacteremia among patients with suspected sepsis. They also highlight, however, the importance of considering each patient individually, as we can use each of these biomarkers more specifically depending on the focus of infection, as well as the most appropriate values in each case to determine the probability of bacteremia [27, 28].

The main limitation of this work is that despite the high number of patients, all came from a single center. In view of this, other studies with a broader approach to patients should be considered, and our data should be contrasted and verified in other centers. Another limitation is that as a retrospective study, the information has been collected from the patients' medical records, which in some cases lacked essential clinical variables.

CONCLUSION

Of the biomarkers analyzed, PCT demonstrated a high predictive power of bacteremia both globally and for each focus of infection analyzed, and its values were significantly increased in the case of GN infections. CRP did not deliver comparable diagnostic performance. In the stratification by focus, the performance of each biomarker as well as their sensitivity and specificity varied importantly.

Conflict of interest
The authors declare that they have no conflict of interest.

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Ethical approval
This work complies with the requirements established in current legislation regarding biomedical research, protection of personal data and bioethics. Permission was requested from the Clinical Research Ethics Committee of the University Hospital "Río Hortega" of Valladolid [Spain], which issued a favorable report [registration code 170/17].

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