

# Request of Acute Phase Markers in Primary Care in Spain

Maria Salinas, PhD; Maite López-Garrigós, MD; Emilio Flores, PhD; Joaquin Uris, PhD; and Carlos Leiva-Salinas, MD

**T**he clinical diagnosis of infectious and inflammatory diseases has classically relied on the patient's history and clinical examination. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are classic acute phase markers that significantly contribute to the diagnosis of such disorders.

The ESR—the rate at which red blood cells sediment in a period of 1 hour—is still a commonly used hematology test, despite its nonspecific measure of inflammation. There has always been a lack of consensus regarding its role as a nonspecific indicator of inflammation and tissue injury. Indeed, a study published in 1994 regarding the clinical value of ESR concluded that guidelines for its rational use were still needed.<sup>1</sup> In 1991, prospective studies<sup>2,3</sup> concluded that the test still deserved a place in the daily routine of the general practitioner (GP) and that the diagnostic value of CRP did not justify replacement of the ESR in daily practice.<sup>4</sup> However, as far back as 1989, by studying the significance of ESR in general practice,<sup>5</sup> it was shown that a multifactorial etiology is usually behind an elevated result. The test remains helpful and is of great value in the diagnosis of some diseases,<sup>6</sup> but its use as a screening test is not supported by the literature.<sup>5,7</sup>

The simultaneous request of ESR and CRP was relatively common in the past, since both are acute phase markers. Today, understanding their individual strengths and shortcomings is important to ensure their correct use. ESR is well established as useful in the diagnosis of many conditions, but it is affected mostly by fibrinogen, which changes slowly in the presence of certain clinical conditions, and increases with age, renal disease, anemia, and some red-cell morphologies. The value of the ESR decreased as new methods were developed to assess inflammatory diseases. CRP is a sensitive and nonspecific inflammatory marker, which is synthesized in response to tissue damage. Learning about a patient's elevated CRP can increase the probability of correctly diagnosing and managing infectious disease, although an elevated

## ABSTRACT

**Objectives:** To study the inter-practice variability in Spain—by institution, management, and regional characteristics—of the frequency and appropriateness of test requests made by primary care practitioners for acute phase markers.

**Study Design:** Observational cross-sectional study.

**Methods:** One hundred forty-one clinical laboratories were invited to participate by providing the number of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC) tests requested by general practitioners. We calculated the ratio of test requests per 1000 inhabitants, ratios of related test requests, and variability index (90th percentile/10th percentile). We compared the results among the different areas according to their setting, location, and management.

**Results:** We recruited 64 laboratories (14,846,065 inhabitants). There were almost twice as many ESR requests as CRP requests; the variability index for ESR was almost double that of CRP. Furthermore, the latter was underrequested in rural-urban areas compared with rural. The ESR/CBC and ESR/CRP ratios are lower in institutions with private management, and the number of ESR requested in institutions with private management are lower than that of public. The differences among Spanish regions were reported for ESR per 1000 inhabitants, ESR/CBC, and ESR/CRP.

**Conclusions:** There was significant variability in the requests made by primary care practitioners for patients' acute phase markers. Rates were influenced by geographic location, hospital setting, and institution management. ESR was inappropriately overrequested; strong efforts should be made to adjust the requests of ESR and to standardize the use of CRP measurement.

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**Take-Away Points**

- Important factors in improving primary care quality in Spain would be decreasing inter-practice variability and paying closer attention to the appropriateness of test requests.
- We present a set of appropriateness indicators about acute phase marker tests in primary care.
- We show laboratory test indicator results of 64 laboratories that served a population of 14,846,065 inhabitants.
- We conclude that the variability in the requesting of tests was strikingly significant and was influenced by geographic location, hospital setting, and institution management.

CRP may also reflect a minor degree of inflammation or certain non-inflammatory conditions.<sup>8</sup> The Spanish guideline<sup>9</sup> for general practice recommends that CRP be measured because it is useful in the majority of primary care patients.<sup>9</sup>

Healthcare utilization and medical practice vary around the world, and have done so for many decades due to differences in population, health status, and patient preferences, among other factors. However, variations not related to patient needs or preferences raise questions regarding the quality and appropriateness of care, as well as efficiency and equity. In disparate regions of Spain, for instance, studies have shown high variability and differences in overall laboratory test requesting by primary care practitioners.<sup>10-12</sup>

The importance of properly diagnosing and managing infectious and inflammatory diseases in the primary care setting, and the crucial role the laboratory plays in doing so, makes it important to investigate the patterns of requesting acute phase markers. The first steps will be to investigate the true variability in test requesting, and to try to identify the root causes behind it.

**METHODS****Data Collection**

Encouraged by previous pilot studies in the Valencian Community region and all around Spain,<sup>11,12</sup> a call for data was posted via e-mail to 141 Spanish hospitals; laboratories were invited to participate by filling out an enrollment form and submitting their results online. Ultimately, we obtained production statistics (number of tests requested by GPs) for the year 2012 from 64 laboratories at different hospitals located throughout Spain's health system (note, the health system in every autonomous community in Spain is divided into health departments, which cover a geographic area and its population and are composed of several primary care centers and usually a unique hospital. The laboratory located at the hospital attends to the needs of every health department inhabitant).

Every patient seen in any primary care center affiliated with these 64 hospital laboratories, regardless of gender, age, or the reason for consultation, was included in the study. Each participating laboratory was required to be able to obtain patient data from local databases and to provide organizational data (ie, population served, public/private management, location). The requests for ESR and CRP measurements were examined in a cross-sectional study. The number of complete blood count (CBC) requests was also collected.

**Data Processing**

After collecting the data, 2 types of appropriateness indicators were calculated: test requests per 1000 inhabitants, and ratio of related test requests (CRP/CBC; ESR/CBC; CRP+ESR/CBC and ESR/CRP). In order to explore the inter-practice variability, another indicator, the "index of variability," was calculated as follows: top decile divided by bottom decile (90th percentile/10th percentile).

We also calculated whether the rate of test requests varied by setting (rural, urban, or rural-urban [ie, part of the inhabitants live in the city and part in the countryside]) of the hospital or by institution management (public vs private).

Finally, the results obtained from the laboratories in the 3 regions with the highest number of departments participating in the study (Valencian Community region: 22 laboratories and 4,703,737 patients; Andalucía: 10 laboratories and 2,791,052 patients; and Castilla y León: 8 laboratories and 1,601,314 patients) were compared among themselves and with the pooled results of the remaining areas (24 laboratories and 5,749,882 patients) to establish whether there were regional differences in the requesting patterns.

**Statistical Methods**

The statistical treatment of the calculated data included: the distribution, the mean, 95% CI for the mean, standard deviation, median, and interquartile range. The analysis of the distribution of the number of test requests per 1000 inhabitants was conducted with the Kolmogorov-Smirnov test.

The differences in the number of test requests per 1000 inhabitants according to the hospital characteristics and per region were calculated using the U Mann-Whitney or Kruskal-Wallis test analysis, as appropriate.

A 2-sided  $P \leq .05$  rule was utilized as the criterion for rejecting the null hypothesis of no difference.

**Table 1. Descriptive Characteristics of Participating Hospitals/Health Departments**

Hospitals/health departments, n	64	
Patients, n	14,846,065	
Population/hospital, mean (95% CI)	231,969.8 (198,487.5-265,452.0)	
Location, n (%)	Valencian Community	22 (34.4%)
	Andalucía	10 (15.6%)
	Castilla y León	8 (12.5%)
	Other regions	24 (37.5%)
Management, n (%)	Public	58 (90.6%)
	Private	6 (9.4%)
	Urban	15 (23.4%)
Setting, n (%)	Rural	3 (4.7%)
	Urban-rural	46 (71.9%)

## RESULTS

We obtained production statistics from 64 laboratories at different hospitals from diverse regions across Spain. Other laboratories did not participate because representatives stated they had difficulties obtaining the requested data from their databases, were not authorized to release the data by the hospital managers, or did not have the time to collaborate. **Table 1** shows a summary of the organizational data of the participating laboratories.

GPs requested 804,524 CRP and 1,340,179 ESR tests during 2012 in a Spanish population of 14,846,065 subjects. **Table 2** shows the descriptive statistical analysis and the variability index for the number of requests per 1000 inhabitants and ratios of related tests. There were almost twice as many ESR as CRP requests. The variability index for ESR was almost double that of CRP.

The variability of the results for the different laboratories studied is shown in the **Figure**. CRP was underrequest-

ed in rural-urban areas, compared with rural (**Table 3**); otherwise, no significant differences were found in test-requesting by GPs in rural, urban, or rural-urban settings. As for variability by institution management, the ratio of ESR/CBC and ESR/CRP indicators were lower in institutions with private management compared with public (**Table 3**). **Table 4** shows the variability of the indicators by region. ESR/1000 inhabitants, ESR/CBC, and ESR/CRP ratios were lower in Valencian Community than in the remaining Spanish regions.

## DISCUSSION

Overall, variability in the requesting of ESR was higher than that of CRP. For some indicators, this variability was influenced by geographic location, hospital setting, and institution management. Lower ESR/CBC and ESR/CRP ratios emerged from privately managed hospitals, suggesting that GPs working in such institutions with new management models are more apt to follow guidelines and to discard old habits. The lower values in ESR/CBC and ESR/CRP results in the Valencian Community might be explained by the presence of a larger number of privately managed hospitals in this region and a significant “appropriateness culture,” since the first studies to compare regional variability were conducted in this community.<sup>10-12</sup> However, it is unclear how these first studies have influenced in the lower values of ESR/CBC and ESR/CRP in the Valencian Community.

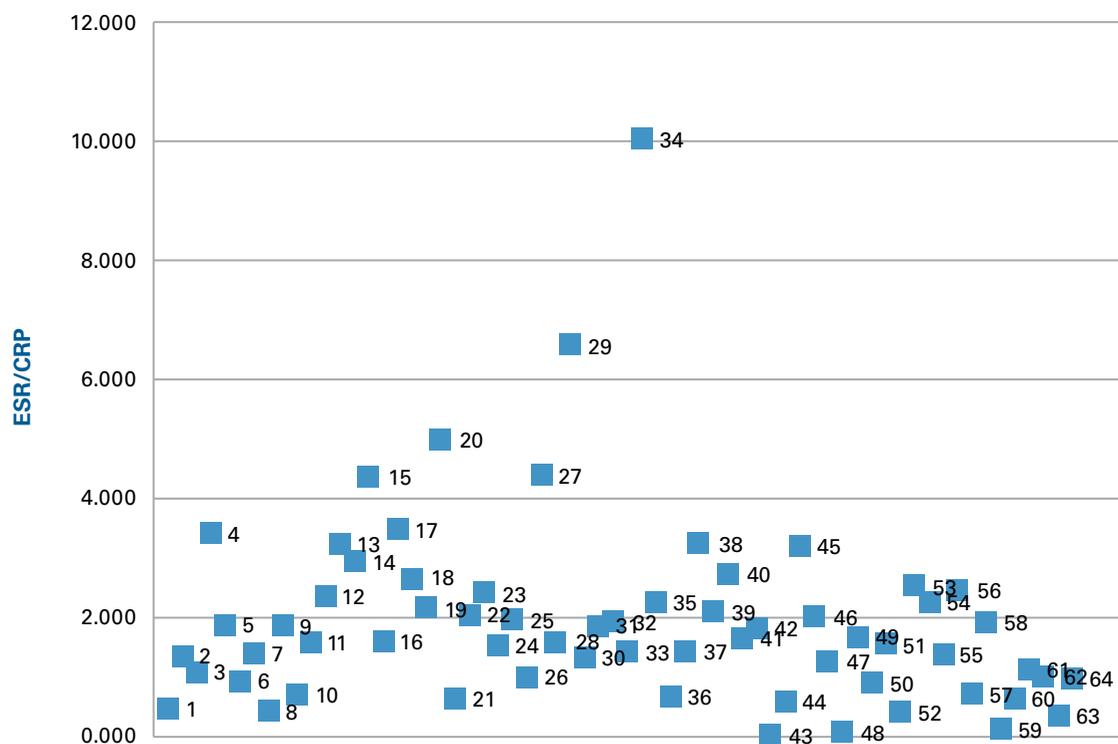
Our results suggest that, despite the absence of clear evidence-based consensus on the relative utility of CRP and ESR, ESR may be overrequested in primary care in

**Table 2. Descriptive Statistical Analysis and Variability Index (90th percentile/10th percentile) of All Indicator Results**

		Mean	95% CI	Median	IQR	Variability Index
Tests/1000 inhabitants	CRP	57.78	48.45-67.12	49.77	35.09-71.31	3.48
	ESR	93.86	79.91-107.81	90.19	57.99-130.12	6.10
	CBC	359.17	340.32-378.02	364.53	324.11-399.94	1.8
Test-request ratios	ESR/CRP	1.69	1.59-2.39	1.68	1.038-2.475	8.26
	ESR/CBC	0.265	0.228-0.302	0.244	0.161-0.349	6.83
	CRP/CBC	0.159	0.137-0.181	0.150	0.104-0.194	3.06
	CRP+ESR/CBC	0.424	0.381-0.466	0.394	0.296-0.541	2.91

CBC indicates complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range.

■ **Figure.** Scattered Plot of “ESR/CRP” Results for Each Laboratory



CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate. Scatter plot shows the ESR/CRP indicator results for each of the 64 laboratories participating in the study.

Spain. While differences in patient case-mix would not seem to account for this overrequesting, differences in patient characteristics may have had an important influence. Additionally, those differences could suggest the existence of different requesting habits or traditions on the part of GPs, which may be difficult to eradicate.

Identifying the reasons behind the overrequesting of ESR tests in primary care is challenging. While a signifi-

cantly elevated ESR is strongly associated with serious underlying diseases,<sup>6</sup> it is also true that an abnormal (ie, slightly and significantly elevated) value with no obvious clinical explanation requires a correct interpretation from the GP who ordered it. In fact, elevation of ESR is not an early sign of malignant disease and does not justify extensive investigation in a patient who has no symptoms to suggest an underlying tumor.<sup>6</sup> In other words, it is key

■ **Table 3.** Differences in Indicators Stratified by Laboratories’ Location and Management

		Tests Requested per 1000 Inhabitants (mean ± SD)		Ratios of Related Tests (mean ± SD)		
		CRP	ESR	ESR/CRP	ESR/CBC	CRP/CBC
Location	Urban	67.57 ± 57.74	75.28 ± 51.72	1.311 ± 0.963	0.204 ± 0.136	0.177 ± 0.141
	Rural	102.18 ± 37.99	132.35 ± 8.79	1.404 ± 0.471	0.285 ± 0.034	0.216 ± 0.069
	Urban-rural	51.69 ± 25.53 <sup>a</sup>	97.41 ± 57.48	2.237 ± 1.741	0.283 ± 0.154	0.150 ± 0.062
Management	Public	55.38 ± 36.68	97.65 ± 56.75	2.123 ± 1.628 <sup>b</sup>	0.278 ± 0.150 <sup>b</sup>	0.156 ± 0.087
	Private	81.01 ± 39.23	57.25 ± 28.39	0.743 ± 0.303	0.136 ± 0.061	0.193 ± 0.087

CBC indicates complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

<sup>a</sup>Significant by Kruskal-Wallis test ( $P < .05$ ).

<sup>b</sup>Significant by U Mann-Whitney test ( $P < .05$ ).

■ **Table 4.** Differences in Indicators Stratified by Laboratories' Region in Spain

	Test per 1000 Inhabitants (mean ± SD)		Ratios of Related Tests (mean ± SD)		
	CRP <sup>a</sup>	ESR	ESR/CRP <sup>a</sup>	ESR/CBC <sup>a</sup>	CRP/CBC
VC	70.58 ± 50.25	71.11 ± 41.905	1.30 ± 0.885	0.19 ± 0.12	0.19 ± 0.12
A	63.40 ± 33.57	85.10 ± 61.015	1.38 ± 0.885	0.24 ± 0.13	0.19 ± 0.06
CL	48.86 ± 18.04	93.21 ± 55.80	1.97 ± 1.14	0.25 ± 0.14	0.14 ± 0.04
OR	46.68 ± 25.54	118.59 ± 58.04	2.92 ± 2.05	0.35 ± 0.15	0.14 ± 0.07

A indicates Andalucía; CBC, complete blood count; CL: Castilla y Leon; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, other regions; VC, Valencian Community.  
<sup>a</sup>Significant by Kruskal-Wallis test ( $P < .05$ ).

to avoid the adverse effects of false positive results.<sup>13</sup> The physician should repeat the test after an appropriate interval rather than pursue an exhaustive search for occult disease.<sup>6</sup> If a GP is unaware of the significance of analytical and biological variation of ESR,<sup>14</sup> meaningless and expensive further testing may result.

In our study, the average ESR/CRP ratio was 1.69—higher than in other studies.<sup>15</sup> Designing and establishing strategies in consensus with GPs to diminish the request of ESR seems necessary. In a prior investigation,<sup>16</sup> the request of ESR tests decreased 60% after such an intervention, CRP requests increased 63.1%, and simultaneous ESR and CRP orders decreased 32.6%. Another study on utilization of common inflammatory markers in new, symptomatic, primary care outpatients based on their cost-effectiveness<sup>17</sup> revealed that CRP testing generated the most useful results, followed by testing of sialic acid, protein fractionation, white blood cell (WBC) count, and ESR. While ESR was poorly correlated with WBC, the combination of CRP and WBC testing was the most cost-effective.

CRP is useful in primary care not only as a diagnostic tool, but also to help decide on antibiotic administration, although the latter is still debated.<sup>18-20</sup> However, the extreme variability in CRP test requests observed in our study indicates that the test was probably over- or under-requested in certain regions. The fact that the CRP+ESR/CBC ratio was close to 1 in certain areas suggests that most patients there had 1 of the 2 tests. On the other hand, the extremely low ratios observed in other regions may reflect an inappropriate management of inflammatory and infectious diseases in primary care. Once again, these results suggest that all stakeholders in the management of infectious and inflammatory disease must communicate to design and establish strategies about the implementation of guideline recommendations and about quality assessment frameworks for better clinical decision making.

## Limitations

Correlating test-ordering by practitioners and the clinical condition of the patients for whom the tests were ordered would have greatly strengthened our findings. Unfortunately, we did not have access to clinical or patient data, which cannot be automatically retrieved from our laboratory information systems. The main limitation of our study is that the differences in ESR and CRP requests among different health departments in Spain could be partly explained by case-mix variations in the different areas, or possible variability in the patient population.

## CONCLUSIONS

Our results highlight the high regional variability in Spain in the requests made by primary care practitioners for classic acute phase markers. The significant differences indicate that additional factors, beyond clinical reasons, could be behind the GPs' test-requesting behavior. ESR was inappropriately overrequested. All stakeholders in the management of infectious and inflammatory disease must communicate to adjust the requesting of ESR and standardize the use of CRP measurement.

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**Author Affiliations:** Hospital Universitario de San Juan de Alicante, Clinical Laboratory Department (ML-G, MS, EF), Alicante, Spain; University of Alicante, Department of Public Health (JU), Alicante, Spain; Neuroradiology Division, University of Virginia (CL-S), Charlottesville.

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**Address correspondence to:** Maria Salinas, PhD, Clinical Laboratory Department, Hospital Universitario de San Juan de Alicante, Carretera Nacional 322. s/n 03550, San Juan, Alicante, Spain. E-mail: salinas\_mar@gva.es.

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