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ORIGINAL RESEARCH

Economic Evaluation of Combined Testing Strategies Using Erythrocyte Sedimentation Rate and C-Reactive Protein Tests

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Objective: To conduct an economic analysis of the use of combined ESR (Erythrocyte Sedimentation Rate) and CRP (C-Reactive Protein) testing strategies compared to CRP testing alone in U.S hospitals.

Methods: A decision tree model was developed to evaluate the cost-effectiveness and cost-benefit of combined ESR and CRP testing compared to CRP alone. The model estimated the laboratory costs, number of misdiagnoses, and follow-up costs associated with misdiagnoses. Model inputs were sourced from published literature and clinical guidelines. Two combined testing strategies were evaluated: 1) result is positive only if both ESR and CRP results are positive (ESR + CRP) and 2) result is positive if either the ESR or CRP result is positive (ESR/CRP). Strategies were evaluated for five individual and three grouped conditions.

Results: Results demonstrated that the ESR + CRP testing strategy is a cost-effective strategy for reducing misdiagnoses and is expected to result in a net cost reduction to the healthcare system when accounting for the reduction in follow-up costs associated with misdiagnoses. In contrast, the ESR/CRP strategy led to increased misdiagnoses when compared to CRP alone.

Conclusion: Results indicate that adopting the ESR + CRP strategy would reduce misdiagnoses and overall costs to healthcare systems.

Keywords: economic analysis, cost-effectiveness and cost-benefit analysis, diagnostic efficiency, ESR, erythrocyte sedimentation rate, CRP, C-reactive protein, in vitro diagnostics

Introduction

Laboratory testing plays a critical role in clinical decision-making for diagnosis and disease management with 70% of medical decisions relying on laboratory tests.[1] Each year, over 14 billion clinical lab tests are conducted in the US and the costs associated with diagnostic testing are estimated to account for over 10% of total US healthcare expenses.[2] Amid concern about increased testing and limited healthcare resources,[3] public awareness campaigns like "Choosing Wisely" have advocated for laboratory testing efficiency and reduced overuse.[4] However, determining whether diagnostic tests are being overused is challenging and requires an evidence-based approach to understand the complex relationships between diagnostic test performance, appropriate use, actual use, and cost-effectiveness.[5]

Erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) are among the most commonly ordered laboratory tests and used to detect inflammation associated with numerous conditions.[6,7] CRP, a plasma protein synthesized by liver cells in response to acute inflammation or infection,[7–9] rises within hours following the onset of infection or inflammation, and returns to normal within three to seven days if the acute condition resolves.[8] In contrast, ESR reflects changes in plasma proteins by measuring the degree to which red blood cells settle in a tube containing anticoagulated blood.[8,10,11] ESR levels tend to increase more slowly, typically within 24–48 hours, are less sensitive to short-term fluctuations, and remain elevated for a longer period.[11] Due to their different kinetic profiles, results are often

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discordant and therefore should not be considered interchangeable.[12] In practice, both tests are routinely ordered by clinicians, raising concerns about the cost of ordering two non-disease specific tests.[6,13,14]

According to one estimate, reducing combined testing with ESR and CRP could save $250,000 −400,000 per year at one large hospital in the U.S.[15] On the other hand, some experts suggest that the combined use of ESR and CRP can play an important role in clinical practice by aiding the physician in diagnosis with differences in the way ESR and CRP measure inflammation providing complementary insights.[6,8,16] For example, ESR has shown superiority in diagnosing conditions such as polymyalgia rheumatica and giant cell arteritis,[17] some malignancies,[18] and lupus.[11] An economic analysis conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) found that combined ESR and CRP testing may be more accurate overall compared to CRP alone, with reductions in misdiagnoses for conditions such as periprosthetic infection, orthopedic infection, inflammatory bowel disease (IBD), and giant cell arteritis.[13]

The economic value of preventing misdiagnoses may vary by whether the misdiagnosis is a false positive or a false negative due to different follow-up costs associated with reaching the correct diagnosis. False positives lead to additional office visits and diagnostics associated with confirming the diagnosis. Costs for these services may be substantial depending on the condition. False negatives lead to additional office visits associated with symptoms and may lead to escalation of disease severity. For some conditions, these additional visits may not be substantial and may not delay diagnosis substantially, while for other conditions the impact can be large.

Technological advancements can influence testing strategies by improving diagnostic accuracy and reducing costs.[19] Recent advancements have led most laboratories to adopt automated methods for ESR, replacing the manual Westergren technique.[20] This shift has made ESR measurement significantly faster, safer, and less labor intensive. Modern ESR and CRP tests are both automated, fast, and inexpensive. The use of ESR in addition to CRP may provide extra information and enhance overall diagnostic accuracy. The aim of this study was to carry out an economic analysis assessing the added value of conducting both ESR and CRP tests together versus conducting the CRP test alone. The study examined the specific research question: what is the cost-effectiveness and cost-benefit of conducting both ESR and CRP tests together versus conducting the CRP test alone.

Methods

An economic model was developed to evaluate the cost-effectiveness and cost-benefit of combined ESR and CRP testing compared to CRP testing alone in the diagnostic work up of patients suspected to have select conditions. The model estimated the laboratory costs (testing costs of ESR and CRP), number of false positives, number false negatives, and follow-up costs associated with misdiagnoses. Patients entered the model upon clinical presentation requiring diagnostic testing. The model time horizon was limited to the point of diagnostic resolution, defined as the point at which a correct diagnosis was achieved and no further diagnostic evaluation was necessary. Discounting was not applied given the short time horizon. The analysis was carried out from the US healthcare system payer perspective and included only direct medical costs incurred by the healthcare system.

Model Structure

The model used a decision tree structure to estimate the diagnostic and cost outcomes of combined ESR and CRP testing compared to CRP alone (Figure 1). The model simulated a cohort of 100 patients. Patients were either tested using CRP only or both ESR and CRP. The model included two methods of using both ESR and CRP: 1) ESR + CRP where the patient is considered positive only if both ESR and CRP results are positive 2) ESR/CRP where the patient is considered positive if either the ESR or CRP result is positive. Patients that truly had the condition were either correctly diagnosed as true positives (TP) or incorrectly diagnosed as false negatives (FN). Similarly, those without the condition were correctly diagnosed as true negatives (TN) or incorrectly as false positives (FP). These diagnosis outcomes were estimated based on the prevalence of the condition and test sensitivity and specificity using the following equations:

1. TP = Condition prevalence × Sensitivity
2. FN = Condition prevalence × (1 – Sensitivity)
3. TN = (1 - Condition prevalence) × Specificity
4. FP = (1 - Condition prevalence) × (1 – Specificity)

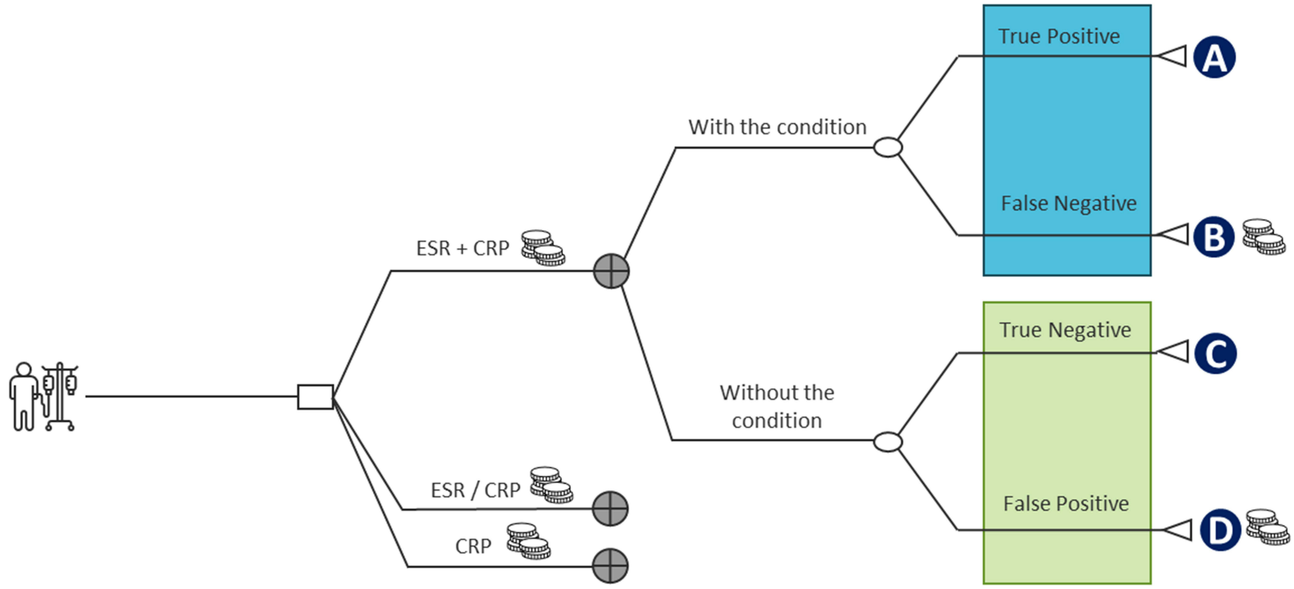

Figure 1 Model Diagram.

Notes: Patient symbol = Patient with undiagnosed symptoms; Coin symbol = cost; ESR + CRP = testing strategy where both ESR and CRP must be positive to be considered a positive diagnosis; ESR/CRP = testing strategy where only one of ESR or CRP must be positive to be considered a positive diagnosis; CRP = testing strategy where only CRP is used; A = No further screening required, and correct treatment received; B = Additional care and testing required to correctly diagnose; C = No additional testing or treatment required; D = Follow-up treatment and testing received that is not required. Blue box indicates that these are determined based on individual or combined test sensitivity and green box indicates that these are determined based on individual or combined test specificity.

Modeled Conditions

Conditions were selected for inclusion in the model based on availability of published data on the diagnostic accuracy of CRP and ESR both individually and in combination. A desk search was conducted between October 2024 and January 2025 to identify existing literature on the diagnostic accuracy (sensitivity and specificity) of ESR and CRP. Five individual conditions and three grouped conditions representing a cross-section of inflammatory conditions were included based on this desk search: rheumatoid arthritis,[21] inflammatory bowel disease (IBD),[22] periprosthetic joint infection,[13] giant cell arteritis,[23] pancreatitis,[24] infection,[14] autoimmune conditions,[14] and cancer.[14]

Clinical Inputs

Inputs for the prevalence of each condition was obtained from published sources. The prevalence values used in the model were not indicative of population-wide prevalence but were specific to the use case for ESR and CRP testing, representing the prevalence of the condition amongst patients being tested for a suspected condition. Table 1 presents the prevalence input values and their sources.

Table 1 Prevalence Inputs, by Condition

Indication	Study Population Prevalence	Source
Rheumatoid Arthritis	38.30%	Shovman 2005[21]
Inflammatory Bowel Disease	20.00%	Otten, 2008[22]
Periprosthetic Joint Infection	42.20%	Assasi et al 2015[13]
Giant cell arteritis	23.17%	Kermani et al 2012[23]
Pancreatitis	30.00%	Pongprasobchai 2010[24]

(*Continued*)

Table 1 (Continued).

Indication	Study Population Prevalence	Source
Infection	2.28%	Watson, 2019[25]
Autoimmune Disorders	3.48%	Watson, 2019[25]
Cancer	1.87%	Watson, 2019[25]

The sensitivity and specificity of each testing strategy for each condition were obtained from published sources and are summarized in Table 2. For rheumatoid arthritis, IBD, giant cell arteritis, infection, autoimmune disorders, and cancer, combined sensitivity and specificity data for ESR + CRP and ESR/CRP were not available from the literature, but sensitivity and specificity of the individual tests were available. Therefore, to estimate the combined diagnostic accuracy for these conditions, a statistical method described by Weinstein et al (2005) was used.[27] This method assumed that ESR and CRP tests are run simultaneously and that their results are independent of each other (ie, the performance of one test does not influence the other). The detailed calculations are further described in the Supplemental Material.

Cost Inputs

The model considered two types of costs: costs of the diagnostic tests used in the testing strategy and follow up costs associated with misdiagnoses. All costs reported are in 2025 US dollars. The costs of diagnostic tests were sourced from Centers for Medicare & Medicaid Services, with an automated ESR and CRP being reimbursed at $2.70 and $5.18 per test, respectively. Follow up costs associated with misdiagnoses were derived based on expected follow up tests and office visits to resolve the misdiagnosis. For false positives, follow up tests were included based on recommendations in US guidelines for each condition and validated by a clinician. It was assumed that a false positive result would trigger a series of additional tests that otherwise would not have been performed. Supplemental Tables S1–S10 in the Supplemental Material provide a detailed outline of these tests and their costs. For false negatives, a cost of $361.31 was assumed for all indications accounting for the expenses of two primary care physician visits and a specialist visit.

Analysis

For each testing strategy, the model estimated the testing cost, misdiagnoses, and follow up costs for a cohort of 100 patients. The combined testing strategies were compared to the strategy with CRP only to assess the incremental impact

Table 2 Sensitivity and Specificity, by Condition and Testing Strategy

Condition	Sensitivity			Specificity			Source
	CRP	ESR + CRP	ESR/CRP	CRP	ESR + CRP	ESR/CRP	
Rheumatoid Arthritis	0.91	0.64*	0.97*	0.38	0.73*	0.21*	Shovman 2005[21]
Inflammatory Bowel Disease	0.77	0.50	0.95*	0.7	0.84	0.47*	Dolwani, 2004[26]
Periprosthetic Joint Infection	0.93	0.87	0.96	0.73	0.85	0.57	Assasi et al 2015[13]
Giant cell arteritis	0.86	0.81	0.98*	0.31	0.41	0.09*	Kermani et al 2012[23]
Pancreatitis	0.86	0.71	1.00	0.9	0.97	0.47	Pongprasobchai 2010[24]
Infection	0.44	0.15*	0.63*	0.79	0.95*	0.61*	Watson, 2019[25]
Autoimmune Disorders	0.49	0.26*	0.76*	0.77	0.95*	0.61*	Watson, 2019[25]
Cancer	0.44	0.19*	0.68*	0.77	0.95*	0.60*	Watson, 2019[25]

Notes: *Combined test performance was not available therefore it was calculated based on statistical estimation described in Weinstein 2005.[27]
Abbreviations: CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate.

of the combined strategy. Cost-effectiveness analysis was conducted by computing the incremental cost-effectiveness ratio as the incremental testing costs divided by the incremental misdiagnoses (cost per misdiagnosis avoided). Additionally, cost-benefit analysis was conducted where the follow up costs associated with misdiagnoses were used to monetize the benefits of reducing misdiagnoses. Cost-benefit was assessed by summing up the incremental testing costs and the incremental follow-up costs. Scenario analyses were conducted to evaluate the impact of varying inputs and assumptions on results. Scenarios included varying testing cost, follow up costs, and sensitivity and specificity values.

An analysis was also conducted to extrapolate the cost-benefit results from the 100-patient cohort to a representative hospital system. Data on the total number of patients tested per hospital was taken from a study of Strong Memorial and Golisano Children's Hospital, which is a 739-bed tertiary care academic medical center that is part of the University of Rochester system.[15] This study found that 46,777 patients were tested with ESR, CRP, or both between December 2010 and November 2011. We divided these patients into suspected conditions based on the distribution of the conditions across ESR and CRP testing observed by Watson et al[25] infection (30%), autoimmune (46%), and cancer (24%). The total annual cost was compared for the strategy using CRP only to strategies using both CRP and ESR to assess the total annual incremental cost of each strategy.

Results

Table 3 presents estimates of the total number of misdiagnoses under each testing strategy, by condition. The ESR + CRP strategy produced fewer misdiagnoses than CRP alone across all conditions. The strategy was estimated to produce more FNs but substantially fewer FPs, which led to a net reduction in total misdiagnoses. The ESR/CRP strategy produced more misdiagnoses than CRP alone across all conditions. It was estimated to produce fewer FNs but substantially more FPs, which led to a net increase in total misdiagnoses.

Table 4 presents estimates of the cost-effectiveness of each combined testing strategy compared to CRP alone, by condition. For the 100-patient cohort, the incremental testing costs of the combined testing strategies was $270. The cost per misdiagnosis avoided with the ESR + CRP strategy ranged from $15.70 for cancer to $61.31 for periprosthetic joint infection with an outlier value of $675.00 for pancreatitis due to its low impact on pancreatitis misdiagnoses. The ESR/CRP strategy was dominated by the CRP strategy for all conditions because it led to more misdiagnoses at a higher cost. Results were robust in scenario analysis (Supplemental Table S11).

Table 5 presents estimates of the cost-benefit of each combined testing strategy compared to CRP alone, by condition. The ESR + CRP strategy resulted in net cost savings for all conditions, ranging from $1,917 savings per 100 patients tested for periprosthetic joint infection to $68,888 savings for cancer. Conditions with expensive follow up testing such as cancer had the greatest net benefit from avoiding these unnecessary follow up costs among FPs. The ESR/CRP strategy

Table 3 Total Number of Misdiagnoses per 100-Patient Cohort, by Condition and Testing Strategy

Condition	CRP			ESR + CRP			ESR/CRP		
	FP	FN	Total Misdiagnoses	FP	FN	Total Misdiagnoses	FP	FN	Total Misdiagnoses
Rheumatoid Arthritis	38.25	3.45	41.70	16.66	13.79	30.45	48.74	1.15	49.89
Inflammatory Bowel Disease	24.00	4.60	28.60	12.80	10.00	22.80	42.40	1.00	43.40
Periprosthetic Joint Infection	15.61	2.95	18.56	8.67	5.49	14.16	24.85	1.69	26.54
Giant Cell Arteritis	53.01	3.24	56.26	45.33	4.40	49.73	69.92	0.46	70.38
Pancreatitis	7.00	4.20	11.20	2.10	8.70	10.80	37.10	0.00	37.10
Infection	20.52	1.28	21.80	4.89	1.94	6.82	38.11	0.84	38.95
Autoimmune Disorders	22.20	1.77	23.97	4.83	2.58	7.40	37.64	0.84	38.48
Cancer	22.57	1.05	23.62	4.91	1.51	6.42	39.25	0.60	39.85

Abbreviations: CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate; FN, false negative; FP, false positive.

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Table 4 Cost-Effectiveness Results of Combined Testing Strategies Compared to CRP Alone for a 100-Patient Cohort, by Condition

Condition	ESR + CRP			ESR/CRP		
	Incremental Misdiagnoses vs CRP	Incremental Testing Cost vs CRP	Cost Per Misdiagnosis Avoided	Incremental Misdiagnoses vs CRP	Incremental Testing Cost vs CRP	Cost Per Misdiagnosis Avoided
Rheumatoid Arthritis	−11.25	$270	$23.99	8.19	$270	Dominated[a]
Inflammatory Bowel Disease	−5.8	$270	$46.55	14.8	$270	Dominated[a]
Periprosthetic Joint Infection	−4.4	$270	$61.31	7.98	$270	Dominated[a]
Giant Cell Arteritis	−6.53	$270	$41.38	14.12	$270	Dominated[a]
Pancreatitis	−0.4	$270	$675.00	25.9	$270	Dominated[a]
Infection	−14.98	$270	$18.03	17.15	$270	Dominated[a]
Autoimmune Disorders	−16.57	$270	$16.29	14.51	$270	Dominated[a]
Cancer	−17.2	$270	$15.70	16.23	$270	Dominated[a]

Notes: [a]Dominated indicates the strategy results in higher costs and worse outcomes.
Abbreviations: CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate.

Table 5 Cost-Benefit Analysis Results of Combined Testing Strategies Compared to CRP Alone for a 100-Patient Cohort, by Condition

Condition	ESR + CRP			ESR/CRP		
	Incremental Follow Up Costs vs CRP	Incremental Testing Cost vs CRP	Net Cost	Incremental Follow Up Costs vs CRP	Incremental Testing Cost vs CRP	Net Cost
Rheumatoid Arthritis	-$11,762	$270	-$11,492	$6,698	$270	$6,968
Inflammatory Bowel Disease	-$39,897	$270	-$39,627	$67,449	$270	$67,719
Periprosthetic Joint Infection	-$2,187	$270	-$1,917	$3,679	$270	$3,949
Giant Cell Arteritis	-$28,947	$270	-$28,677	$63,600	$270	$63,870
Pancreatitis	-$3,415	$270	-$3,145	$29,448	$270	$29,718
Infection	-$5,753	$270	-$5,483	$6,585	$270	$6,855
Autoimmune Disorders	-$6,311	$270	-$6,041	$5,527	$270	$5,797
Cancer	-$69,158	$270	-$68,888	$65,313	$270	$65,583

Abbreviations: CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate.

resulted in an increase in net costs due to the increase in misdiagnoses when using this strategy. Results were robust in scenario analysis (Supplemental Table S12).

Table 6 presents estimates of the cost-benefit of each combined testing strategy compared to CRP alone for a representative hospital. The ESR + CRP strategy resulted in net cost savings for all conditions totaling $9.95 million annually, which was primarily driven by cost savings from patients tested for suspected cancer. The ESR/CRP strategy resulted in an increase in net costs of $9.7 million due to the increase in misdiagnoses when using this strategy.

Table 6 Cost-Benefit Analysis Results for a Representative Hospital, by Condition and Testing Strategy

Condition	ESR + CRP			ESR/CRP		
	Incremental Follow Up Costs vs CRP	Incremental Testing Cost vs CRP	Net Cost	Incremental Follow Up Costs vs CRP	Incremental Testing Cost vs CRP	Net Cost
Infection	-$804,150	$37,740	-$766,410	$920,446	$37,740	$958,187
Autoimmune Disorders	-$1,346,435	$57,604	-$1,288,831	$1,179,170	$57,604	$1,236,774
Cancer	-$7,928,515	$30,954	-$7,897,561	$7,487,711	$30,954	$7,518,665
Total	-$10,079,100	$126,298	-$9,952,802	$9,587,327	$126,298	$9,713,625

Abbreviations: CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate.

Discussion

This study evaluated the incremental cost-effectiveness of combined ESR and CRP testing strategies across a range of five individual conditions and three grouped conditions. The results demonstrated that the ESR + CRP testing strategy is a cost-effective strategy for preventing misdiagnoses and is expected to result in a net cost reduction to the healthcare system when accounting for the reduction in follow-up costs associated with misdiagnoses. In contrast, the ESR/CRP strategy led to increased misdiagnoses when compared to CRP alone along with increased costs. These results highlight the benefits of using a combined testing strategy and the importance of using the correct approach for the combined strategy.

While there have been recent calls for healthcare systems to use only CRP when testing for inflammation in order to reduce spending,[4] advances in ESR technology have substantially reduced the burden of the test on healthcare resources.[28] However, even the older ESR method was not costly, so the question that must be answered is what diagnostic value is gained for the additional cost and is that value worth it. The results of this study indicated that for the ESR + CRP strategy, the diagnostic value is worth the additional cost of the ESR test, resulting in a net cost saving to the healthcare system. It was estimated that for a representative hospital, cost savings would be $9.95 million annually. The kinetics of CRP and ESR are different therefore test performance can vary based on condition and disease severity, so the use of both tests can be complementary. There may still be cases where only one test is needed, but results of this study indicate that there is value to including both tests when diagnosing many conditions.

To our knowledge there has only been one previous study conducting economic analysis of combined testing strategies with CRP and ESR. This study, conducted by CADTH, found similar results in the Canadian context to those presented here for the US context.[13] In addition to demonstrating similar conclusions about resource use for the US context, the present study included additional conditions and incorporated cost-benefit analysis in addition to cost-effectiveness analysis to aid healthcare systems in decision-making about resource use.

This study is subject to several limitations. First, ESR and CRP are non-specific and often among many tests doctors use in the diagnostic process alongside clinical examination. Further, it is difficult to determine what other factors and tests influence doctors' decisions when making a diagnosis. In this study, estimates of diagnostic accuracy are based on published literature assessing the diagnostic accuracy of ESR and CRP individually, which may be a simplification of reality. Second, in cases where the diagnostic accuracy of the combined ESR and CRP strategies were not available from the literature and so had to be calculated using published methods, it was necessary to assume independence between performance of the two tests. This assumption may not hold in all cases, which will affect the diagnostic performance of combined tests. Third, there may be important differences between false positives and false negatives that make combining them into one measure of misdiagnoses unhelpful. We attempted to address this limitation in cost-benefit analysis by putting a cost value to each false positive and false negative. However, the analysis only captured a snapshot from the point of diagnosis and accounts only for the work-up costs, so it may not account for the full long-term implications of misdiagnoses, such as the added complications due to false-negative results. Additionally, this costing assumes that follow-up testing due to misdiagnosis is completely wasteful, which may not be the case if there are other clinical benefits to these follow-up tests. Additionally, test performances may vary by the prevalence of the conditions, which may limit the generalizability of diagnostic accuracy estimates. Finally, the extrapolation of results to a representative hospital relied on historical utilization data that may not fully reflect current practice. Therefore, these results may not be generalizable.

Conclusion

The results of this study demonstrate that the value of combining ESR with CRP testing is worth the minimal additional cost when using an appropriate testing strategy, particularly now that both tests pose minimal burden to laboratory resources. The ESR + CRP testing strategy was estimated to have a minimal cost per misdiagnosis avoided and results in cost savings to the healthcare system by reducing follow-up costs related to misdiagnoses. In contrast, the ESR/CRP testing strategy was estimated to increase misdiagnoses and increase costs. Results therefore indicate that adopting the ESR + CRP strategy would reduce misdiagnoses and overall costs to healthcare systems.

Data Sharing Statement

No datasets were generated in connection with this study.

Ethics/Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conflict of Interest.

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