Global Academic Nursing Journal

REVIEW ARTICLE

Clinical utility of Point-of-Care D-dimer assay analyzers to exclude pulmonary thromboembolism in patients with COVID-19

Utilidad clínica de los analizadores de ensayo de dímero D en el lugar de atención para excluir la tromboembolia pulmonar en pacientes con COVID-19

Utilidade clínica de analisadores de ensaio D-dímero Point-of-Care para exclusão de tromboembolismo pulmonar em pacientes com COVID-19

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How to cite this article:
Silva RCL, Souza IV, Peregrino AAF, Pessanha CM, Meireles IB, Silva CRL. Clinical utility of Point-of-Care D-dimer assay analyzers to exclude pulmonary thromboembolism in patients with COVID-19. Glob Acad Nurs. 2020;1(3):e58. https://dx.doi.org/10.5935/2675-5602.20200058

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Submission: 10-07-2020
Approval: 10-14-2020

Abstract

The aim was to evaluate the clinical utility of D-dimer POC assay analyzers to rule out the diagnosis of PTE in adult patients diagnosed with COVID-19. Systematic review and meta-analysis. The evaluated technology was the Point-of-Care D-dimer assay analyzer. To combine the effect estimates whose measure was the difference between the means, the random effect model was used. We included 10 studies that evaluated 14 Point-of-Care analyzers compared to the Enzyme Linked Immunosorbent Assay. All Point-of-Care analyzers evaluated showed sensitivity and NPV greater than 95 and 97%, respectively, with an average return time of 95 minutes. Evidence suggests that the use of Point-of-Care analyzers for D-dimer is clinically useful to rule out cases of pulmonary thromboembolism and other thromboembolic complications in patients with COVID-19 treated in the emergency room or in primary care units.

Descriptors: Blood Clotting Disorders; Blood Clotting Tests; Pulmonary Embolism; Enzyme Immunoadsorption Tests; Point-of-Care Tests; Coronavirus Infection.

Resumén

El objetivo fue evaluar la utilidad clínica de los analizadores de ensayo POC de dímero D para descartar el diagnóstico de TEP en pacientes adultos con diagnóstico de COVID-19. Revisión sistemática y metaanálisis. La tecnología evaluada fue el analizador de ensayo de dímero D Point-of-Care. Para combinar las estimaciones del efecto cuya medida fue la diferencia entre las medias, se utilizó el modelo de efectos aleatorios. Se incluyeron 10 estudios que evaluaron 14 analizadores de punto de atención en comparación con el ensayo de ensayo inmunoabsorbente ligado a enzimas. Todos los analizadores Point-of-Care evaluados mostraron una sensibilidad y VPN superiores al 95 y 97%, respectivamente, con un tiempo de retorno promedio de 95 minutos. La evidencia sugiere que el uso de analizadores de punto de atención para el dímero D es clínicamente útil para descartar casos de tromboembolismo pulmonar y otras complicaciones tromboembólicas en pacientes con COVID-19 tratados en la sala de emergencias o en las unidades de atención primaria.

Descriptores: Trastornos de la Coagulación Sanguínea; Pruebas de Coagulación Sanguínea; Embolia Pulmonar; Pruebas de Inmunoadsorción Enzimática; Pruebas de Punto de Atención; Infección por Coronavirus.

Resumo

Objetivou-se avaliar a utilidade clínica de analisadores de ensaio D-dímero POC para afastar o diagnóstico de TEP em pacientes adultos com diagnóstico de COVID-19. Revisão sistemática e meta-análise. A tecnologia avaliada foi o analisador de ensaio D-dímero *Point-of-Care*. Para a combinar as estimativas de efeito cuja medida foi a diferença entre as médias, utilizou-se o modelo de efeito randômico. Foram incluídos 10 estudos que avaliaram 14 analisadores *Point-of-Care* comparados ao ensaio *Enzyme Linked Immunosorbent Assay*. Todos os analisadores *Point-of-Care* avaliados apresentaram sensibilidade e VPN superior a 95 e 97% respectivamente, com tempo de retorno do exame em média 95 minutos menor. As evidências sugerem que os uso de analisadores *Point-of-Care* para D-dímero tem utilidade clínica para afastar casos de tromboembolismo pulmonar e outras complicações tromboembólicas em pacientes com COVID-19 atendidos em sala de emergência ou em unidades de atendimento de Atenção Primária.

Descritores: Transtornos da Coagulação Sanguínea; Testes de Coagulação Sanguínea; Embolia Pulmonar; Ensaios de Imunoadsorção Enzimática; Testes Imediatos; Infecção por Coronavírus.

Introduction

Acute pulmonary thromboembolism (PTE) is a potentially fatal disease, the incidence of which has been increasing in recent years, although lethality is decreasing, possibly due to improved diagnostic and treatment strategies[1].

Studies on its epidemiology in Brazil are scarce and based on autopsy data, with an estimated prevalence of 3.9% to 16.6%. Between 1989 and 2010, 92,999 deaths due to PTE were reported as a basic cause in the country[2-4].

The PTE is the most feared acute complication of deep vein thrombosis, being the most common cause of preventable deaths in hospitalized patients. This cause of pulmonary embolism may be associated with 5 to 10% of deaths in hospitalized patients. Approximately 25% of all cases of venous thromboembolism are associated with hospitalization and of these, 50 to 75% occur in clinical patients[4-6].

The rate of PTE without clinical suspicion before death is still extremely high, ranging from 67 to 91%, even with all the improvements that have been observed in terms of diagnostic resources and the advancement of knowledge about the pathophysiology and management of the disease. Therefore, it is known that when the diagnosis is not established, the mortality rate due to PTE is high, reaching around 30%, which is since treatment is impossible[6,7].

The risk of venous thromboembolism in patients with COVID-19 is not yet properly documented, which is why it is necessary to assess the risks of the patient presenting this thromboembolic complication, considering the signs and symptoms they present on physical examination.

Hypercoagulability has been observed in patients infected with the new coronavirus, characterized by increased levels of fibrinogen and D-dimer, and changes in coagulation pathways, particularly among patients with the severe form of the disease (SRAG). Rapid identification of those at high risk is essential to promptly provide them with adequate prophylaxis and treatment to reduce the morbidity and mortality attributed to this disease[8-17].

The risk of PTE among patients infected by COVID-19 has been of great concern in Brazil and worldwide, causing a substantial increase in the performance of imaging tests. For patients with unexplained abrupt worsening in PaO2 / FiO2 and hemodynamic instability, in suspected cases of acute deep vein thrombosis (DVT) and pulmonary embolism (PE), ultrasound confirmation of the lower extremities and pulmonary angiography by tomography is recommended. computerized (CT), respectively, are not always possible to be performed in emergency rooms or in primary care units, which can delay the start of appropriate treatment[18,19].

In patients with suspected venous thromboembolism (VTE), D-dimer levels may be particularly useful for diagnostic exclusion although they may be elevated in the presence of other causes of fibrin formation. D-dimer levels are particularly high in critically ill patients with COVID-19 admitted to intensive care units and especially among non-survivors (which suggests that D-dimer can be used as a prognostic marker in the disease, tests for it to be performed initially on all hospitalized patients[14,19-21].

The usefulness of D-dimer assays to exclude VTE has been emphatically demonstrated in the last 10 years, which is why it has been used as a laboratory routine in health services. The indirect enzyme immune assay - ELISA (from English Enzyme-Linked Immunosorbent Assay) - is considered the reference standard for the quantification of D-dimer. This method involves loading plasma samples into microtiter microwells coated with antibodies that have high binding affinity for D-dimer. After incubation, a labeled antibody is then added, and the amount of bound and labeled substance is measured using a colorimetric reaction[22].

The ELISA assay has high sensitivity and specificity, but it is complicated, time-consuming and requires intense labor and can usually only be performed in laboratories during working hours. In addition, the intensive and time-consuming restrictions typical of these trials make them impractical for routine clinical laboratory use in emergency rooms and particularly as an examination to rule out the diagnosis of VTE (or PTE) and disseminated intravascular coagulation (ICD)) in patients with COVID-19, giving space for the incorporation of faster, automated and highly sensitive assays to be used as Point-of-Care assay analyzers[22,23].

There is no published Clinical Guideline or Scientific Technical Opinion (PTC) in Brazil on the usefulness of quantitative D-dimer tests, to be used in emergency rooms or any other sector of the hospital, or even specific patient profiles. patient. The possibility of accessing the results of examination of biomarker dosages of other pathologies involved in COVID-19, such as, for example, D-dimer for thrombotic events, CRP for infection or inflammation, and procalcitonin for bacterial co-infection and sepsis, in less time possible, puts Point-of-Care (POC) analyzers as possible alternatives to improve future forecasts for a more general population, in addition to those infected with COVID-19[23-25].

There are only 4 brands of POC D-dimer test analyzers duly registered (and commercialized) in Brazil: AQT 90 FLEX®, manufactured by Radiometer, from Denmark (ANVISA No. 10301160185); Pathfast D-Dimer®, manufactured by Japan's Mitsubishi Chemical Medicine Corporation (ANVISA No. 10071770613); Stratus CS Stat®, manufactured by the company Siemens Healthcare Diagnostic, from the United States of America (ANVISA No. 10345161924); and Nycocard Reader II®, manufactured by Abbott Diagnostics Technologies in Norway (ANVISA No. 10071770765).

The technology of POC analyzers is in the initial diffusion phase AT THE NATIONAL SCENARIO and is not yet part of the list of technologies of the Unified Health System (SUS) nor of the National Supplementary Health Agency (ANS), although it is already available and marketed through some commercial representatives in the country. They are registered as products that present medium risk to the user or patient and low risk to public health.

The objective of this study was to evaluate the

clinical utility of D-dimer POC assay analyzers to rule out the diagnosis of PTE in adult patients diagnosed with COVID-19.

Methodology

It is a systematic review with meta-analysis, cut from a Technical-Scientific Opinion (PTC) developed by the team of researchers, which is why the review protocol was not submitted for registration with PROSPERO. In the description of the study, the checklist proposed by PRISMA Flow was used. The research question was: For adult patients diagnosed with COVID-19 who have a suggestive but unlikely clinical picture of pulmonary thromboembolism (Wells nucleus ≤ 4), the use of POC D-dimer assay analyzers is clinically useful to rule out the diagnosis?

The question was structured by the acronym PICO as follows: Population - Adult patients diagnosed with COVID-19 who present suggestive clinical picture, but unlikely to have pulmonary thromboembolism (Wells nucleus ≤ 4); Intervention - POC D-dimer assay analyzers; Comparator - D-dimer assay analyzer Enzyme Linked Immunosorbent Assay (ELISA); Outcomes: Primary - Sensitivity and Negative Predictive Value (VPN); Secondary - Time to return the exam result and ease of use.

The outcomes were defined based on the clinical history of thromboembolic complications, in the opinion of experts and based on the scientific literature that deals with the evaluation of the performance of diagnostic tests, whose objective is to determine whether a test is useful in practice by evaluating, among other things, intrinsic and extrinsic parameters of the test and feasibility, as well as their effects on clinical decisions and outcomes.

In this perspective, the primary outcome was defined as being the most appropriate to assess the clinical utility of the test analyzed, understanding that the sensitivity and NPV of a test are the two most relevant variables for assessing the clinical utility of D-dimer trials to rule out diagnostic hypothesis of PTE, using the test result as a complement to the Wells score.

Secondary outcomes were defined as the most appropriate for assessing the usability and costs associated with using POC analyzers. Therefore, assessing possible changes in diagnostic suspicion, changes in patient care routes and flows and, above all, the time to return the test result and time to start definitive treatment, are also essential to assess the clinical usefulness of the technology.

The eligibility criteria for inclusion and exclusion of studies were defined based on the research question structured by the acronym PICO. Therefore, articles were included whose population studied was formed by adult patients, without upper age limit, with suspicion of DVT, PTE, PE or ICD, with different underlying diseases, treated in emergency rooms or in primary care units.

Regarding the evaluated technology, studies were included that evaluated quantitative and qualitative analyzer devices for testing D-dimers for use in points of care, in primary care services and in emergency care units and inpatient care units. and high complexity.

Regarding comparators, studies that evaluated central laboratory analyzers for quantitative, semi-quantitative and qualitative D-dimer assays using the ELISA method were included, in primary care services and in emergency care units and medium and inpatient units. high complexity.

As inclusion criteria in relation to the study designs, priority was given to: systematic reviews, randomized and non-randomized clinical trials, competing and non-competing cohort studies, complete and partial economic assessments, clinical guidelines and technical-scientific opinions, economic assessments in health and cross-sectional studies of diagnostic accuracy, published in English, Spanish or Portuguese, available in full texts and without limitations related to the year of publication.

The choice of the design of the eligible studies considered not only their research question, but also the hierarchy of scientific evidence and the way in which the articles were planned and conducted to answer their respective research questions. In this sense, priority was given to studies with better methodological quality and those that could be useful in the analysis of the clinical utility of a diagnostic test.

The definition of sources and search strategies for retrieving information in the scientific literature was designed to guarantee a broad and broad view of the best scientific evidence available to answer the research question.

They were consulted from August 28 to September 9, 2020, observing the eligibility criteria, the Medline bases (via PUBMED); Embase; Cochrane; ECRI Institute; VHL; CAPES and Google Scholar Theses and Dissertations Portal.

The controlled terms used in the search strategies were defined according to the PICO arms (Chart 1). The intersection of the outcomes arm with the other PICO arms was not considered to allow a more sensitive search possible in the search strategies (Appendix).

Chart 1. Controlled terms and synonyms used in the construction of search strategies, using the acronym PICO. Rio de Janeiro, RJ, Brazil, 2020

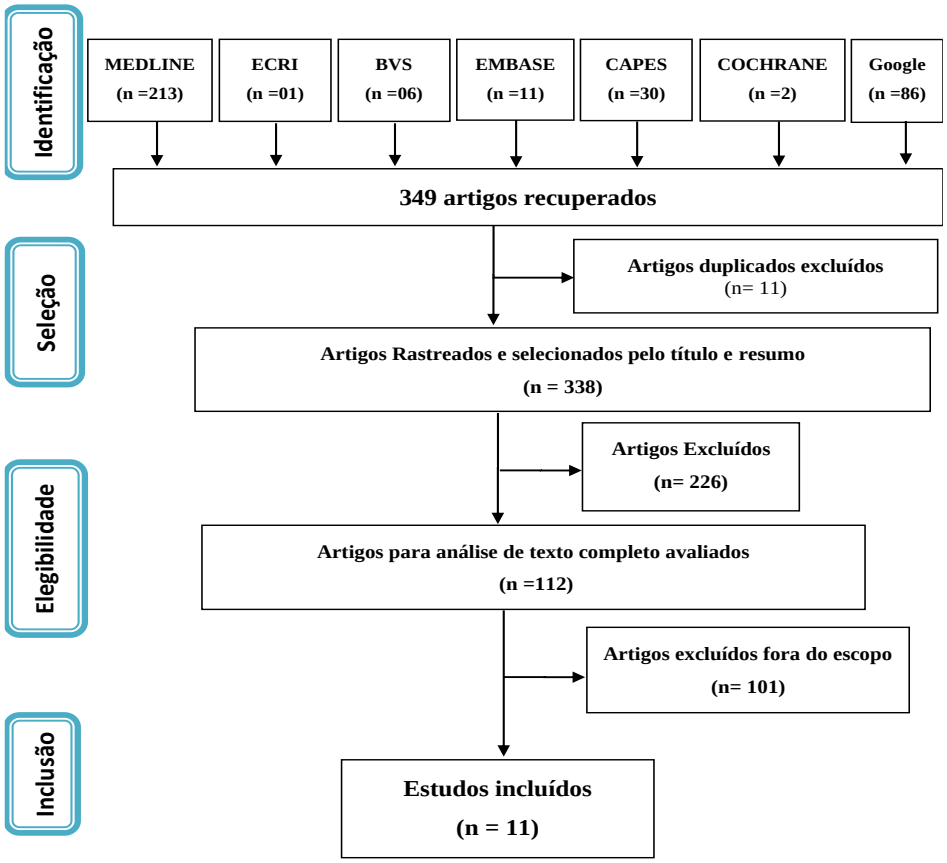
PICOS	DeCS	MeSH	Emtree
Population	Embolia Pulmonar; Tromboembolia Pulmonar; Tromboembolismo Pulmonar; Tromboembolia Venosa; Tromboembolia	*Pulmonary Embolism; Embolism, Pulmonary; Embolisms, Pulmonary; Pulmonary Thromboembolisms; Pulmonary Thromboembolism; Thromboembolism, Pulmonary; Thromboembolisms, Pulmonary*	*lung embolism; Thromboembolism; venous thromboembolism deep vein thrombosis*

Intervention	D-dímero (não controlado); Sistemas Automatizados de Assistência Junto ao Leito; Tecnologia de Assistência Junto ao Leito	*D dimer; Point-of-Care Systems; Point of Care Technology; Point-of-Care*	*Point of care testing; D dimer assay; D dimer*
Control	Ensaio de Imunoadsorção Enzimática; ELISA; Ensaio Imunoadsorvente Enzima-Associado; Ensaio Imunoadsorvente Ligado à Enzima; Ensaio de Imunoadsorção Ligado à Enzima	*Enzyme-Linked Immunosorbent Assay; Assay, Enzyme-Linked Immunosorbent; Assays, Enzyme-Linked Immunosorbent; Enzyme Linked Immunosorbent Assay; Enzyme-Linked Immunosorbent Assays; Immunosorbent Assay, Enzyme-Linked; Immunosorbent Assays, Enzyme-Linked; ELISA*	*Immunoassay* *Enzyme Linked Immunosorbent Assay*

In the process of retrieving information until the inclusion of articles according to the eligibility criteria, the recommendations of the PRISMA Flow Diagram were followed, paying attention to its four stages: Identification, Selection, Eligibility and Inclusion[26].

The PRISMA flowchart (Figure 1) shows the number of documents / articles retrieved during the search in the databases consulted. The strategies developed for each search resulted in 213 documents retrieved from Medline (via PUBMED Portal), 11 from Embase, 02 from Cochrane, 06 from VHL, 01 from ECRI Institute, 30 from CAPES Dissertations and Theses Portal and 86 documents from Google Scholar.

Figure 1. Flowchart of article selection (Prisma Flow). Rio de Janeiro, RJ, Brazil, 2020



The risk of bias in observational studies was assessed using Cochrane's Risk of Bias (ROB) tool using RevMan® 5.4.1 software. Graph and summary of risk of bias were plotted using the same software. Systematic reviews were assessed by AMSTAR-2.

Results

A total of 349 documents were recovered. After eliminating 11 duplicate documents, 338 were screened and evaluated by title and abstract. A total of 226 documents were excluded for methodological problems, related to the

designs, or for not meeting the eligibility criteria. Most of these documents were retrieved from Capes and Google Scholar's Dissertations and Theses portal. For reading in full text, 112 documents remained, of which 101 were excluded because they were outside the scope of the research. A total of 11 documents were included in the meta-analysis.

Of the 11 documents included, 04 are cross-sectional studies to assess diagnostic accuracy, 03 systematic reviews, 04 prospective observational studies. All studies were carried out outside Brazil (Chart 2).

The evaluation by AMSTAR-2 indicated that 02 systematic reviews showed moderate methodological quality and 01 critically low (Appendix).

Regarding the observational studies of diagnostic accuracy of the POC assay analyzers, the result of evaluating the quality of the studies included in the review (Figures 2 and 3) shows that the risk of bias should be considered as high, especially due to the risk of bias relative to the patient selection and allocation process, the lack of randomization and the lack of blinding, especially at the level of outcome assessors.

Only a single study clearly presented the criteria used for patient selection, including randomization, and blinding at least at the level of outcome assessors.

Figure 2. Summary of Cochrane risk of bias. Rio de Janeiro, RJ, Brazil, 2020

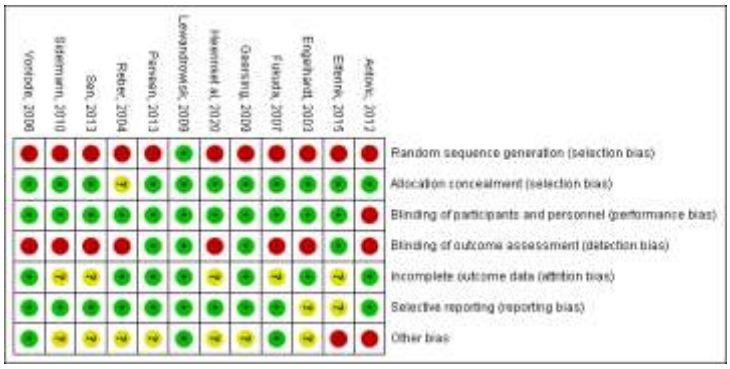


Figure 3. Cochrane bias risk graph. Rio de Janeiro, RJ, Brazil, 2020

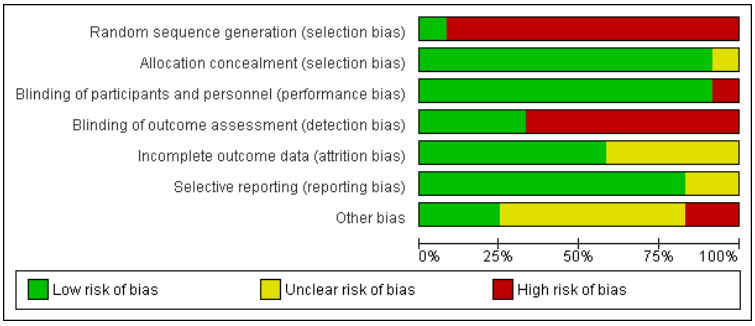


Chart 2. Summary of data extracted from the studies. Rio de Janeiro, RJ, Brazil, 2020

Authors	Objective	Method	Result
Reynen 2017	Evaluate the clinical utility of D-dimer POC	Systematic review limited to an English document published between January 1, 2012 and October 17, 2017.	A systematic review is included. POC sensitivity was 94% to 95% (Wells ≤4) and 97% (Wells <2). The VPN was 94% to 99% (Wells ≤4) and 99% (Wells <2).
Antovic 2012	Compare 5 POC D-dimer	Accuracy Cross with 60 blood samples were analyzed.	Using 0.5lg / mL as the cutoff value, the agreement between Pathfast® and Tinaquant® (K) = 0.81, P <0.0001). The agreement between Tinaquant® and Cardiac® was k = 0.72. For Stratus® (k = 0.94) and VIDAS® (k = 0.92). With NycoCard® (cutoff point, 0.3 lg / mL) the agreement was k = 0.24, and the CV was 41%. The CV for the other four investigated trials was <12%.

Perveen 2013	Compare POC VIDAS® D-dimer and AQT90 FLEX®	Prospective Observational with 104 patients.	The average time for D-dimer by VIDAS® was 258 min ([IQR], 173-360) and by POC of 146 min (IQR, 55-280.5); the median time difference was 101.5 min (IQR, 82-125.5). Sensitivity of 83.3% (70.4 to 91.3%); specificity, 100% (93.6-100%).
Sem 2013	Evaluate the POC Alere Triage®	Prospective with 100 patients. 2-month follow-up.	The response time of the D-dimer decreased by 83% with the POC. Median levels of POC D-dimer showed good correlation between patients with positive D-dimer and Wells score.
Vonlode 2006	Rate POC Innotrac Aio!®	Cross-section of Accuracy with 525 apparently healthy patients.	The VPN and VPP were 99.1% and 55.1% (0.6 mg / L) and 95.9% and 68.3% (1.0 mg / L), with test efficiencies of 74.9% and 84.5%, respectively.
Geersing 2009	Evaluate clinical utility of D-dimer POC	Prospective with 577 patients in primary care units with DVT signs and symptoms the Technicians were blinded.	All POCs had a VPN of more than 98%, with sensitivity ranging from 91% for Clearview Simplify® to 99% for Vidas®, and the time for results ranged from 10 minutes (Clearview Simplify®) to 38 minutes (VIDAS®) . Usability analysis were comparable.
Elferink 2015	Evaluate the clinical utility of 8 POC D-dimer	Transversal of Accuracy with 290 primary care patients suspected of DVT.	The sensitivity of the tests was on average greater than 95% 95% CI (78 - 100%) for quantitative POC and 91% 95% CI (72 - 99%) for qualitative POC. With a low prevalence of proximal DVT (8.2%), all tests reached a VPN of at least 99%.
Reber 2004	Evaluate the performance of the POC Stratus CS D-dimer ®	Prospective observational with 1102 patients suspected of DVT or EB.	With a cut-off point of 400 ng / ml FEU, sensitivity, specificity and NPV exclusion were 96.5% 95% CI (90.1 to 99.3), 46.3% 95% CI (39.4 to 53.2) and 95% CI 96.9% (91.3 to 99.4), respectively. A 300 ng / ml cutoff resulted in even greater sensitivity and VPN.
Geersing 2009	Assess the clinical utility of POC for D-dimer	Systematic review. Bivariate regression to examine sources of variation and to estimate the sensitivity and specificity of the tests.	23 studies and 13,959 patients were included in the meta-analysis. The combined sensitivity and specificity of all studies was 0.88 95% CI (0.83 to 0.92) and 0.70 95% CI (0.62 to 0.77), respectively.
Lewandrowisk 2009	Assess the impact of implementing a D-dimer POC test	Cross-sectional with 363 patients. All paired samples were collected simultaneously.	The D-dimer turnaround time (from blood draw to result) decreased by approximately 79% (from 120 minutes to 25 minutes).

Quantitative overview

In the 11 studies included in the review, 08 evaluated the clinical usefulness of using POC analyzers for D-dimer assays in terms of sensitivity and negative predictive value and other 03 studies, in relation to time for the return of the exam result. All studies were carried out outside Brazil. In all, 14 brands of quantitative, qualitative, and semi-quantitative POC D-dimer assay analyzers were evaluated (Appendix).

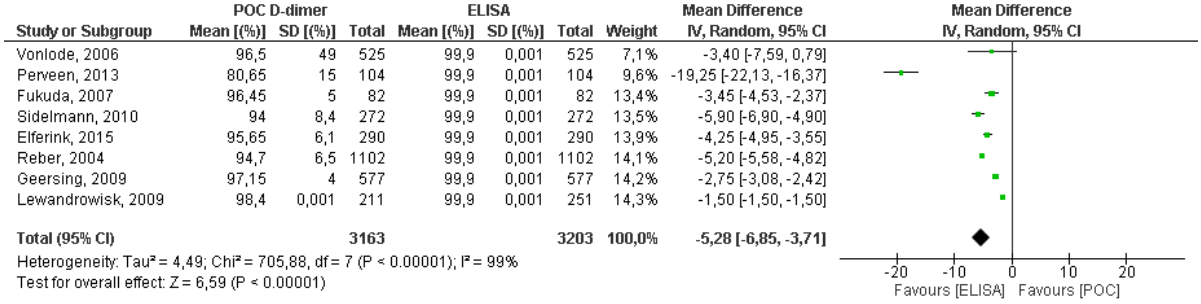
The heterogeneity of the included studies was identified by visual inspection of the graphs of the meta-analysis, or by the chi-square test. Quantification of heterogeneity was analyzed by the I^2 test, whose results can vary from 0% to 100%, with a 95% confidence interval, to demonstrate the percentage of total variation between studies due to heterogeneity, being, therefore, the best estimate used to assess the consistency of the evidence. Statistically significant heterogeneity is considered when I^2 is greater than 50% and p value is less than 0.10[27].

Sensitivity and Negative Predictive Value

Quantitative tests have proven to be more accurate, and probably, for this reason, may be more useful in emergency services. Some manufacturers provide analyzers that can be used for a range of biomarkers and may be useful for analyzing a variety of analytes routinely requested for patients seen at these services.

The concentrations of D-dimer obtained in blood stabilized with citrates are comparable to those recorded in blood stabilized with heparin or EDTA. The fact of being able to use whole blood gives even more agility in the return time of the test result. The tests proved to be robust because variation in the cut-off values from 0.35 to 0.50 mg / L are practically without effect on NPV. The combination of the estimates resulted in an average sensitivity of the POC assay analyzers for D = Dimer greater than 95% (Figure 4).

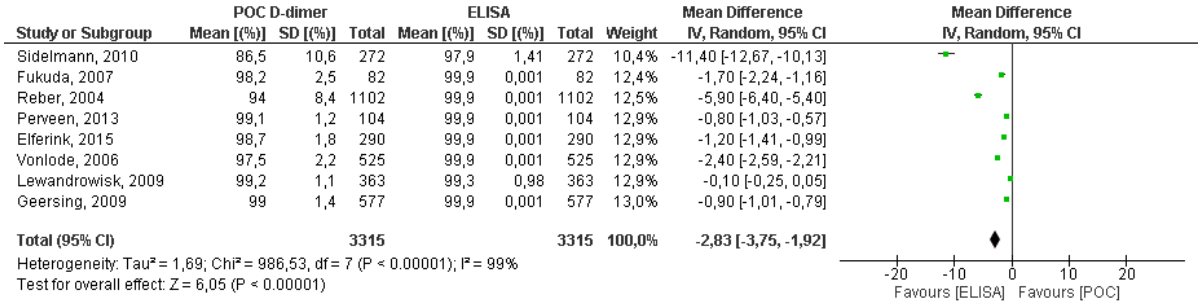
Figure 4. Forest Plot of the meta-analysis of the combination of sensitivity estimates from POC tests compared to ELISA. Rio de Janeiro, RJ, Brazil, 2020



Note: Analysis using the difference between the means with a confidence interval of eight prospective and retrospective observational studies. As the rhombus does not include the corresponding vertical line, the nullity of the effect (zero) means that, in this comparison, the difference between the means was statistically significant, and as the I^2 was 99%, then the meta-analysis does not reject the hypothesis of heterogeneity.

All POC assay analyzers evaluated showed NPV greater than 97%, which can be considered particularly good when it is intended to rule out a diagnostic hypothesis, suggesting, therefore, that there is evidence that these analyzers are sufficiently accurate so that they can have clinical utility as a diagnostic system. screening in combination with preclinical scores. Thus, they constitute a valuable tool for the exclusion of complications related to hypercoagulability, especially VTE in symptomatic patients and classified as low risk by the Wells scale, whether in the emergency room or in primary care, regardless of their disease. base (Figure 5).

Figure 5. Forest Plot of the meta-analysis of the combination of negative predictive value estimates from POC tests compared to ELISA. Rio de Janeiro, RJ, Brazil, 2020

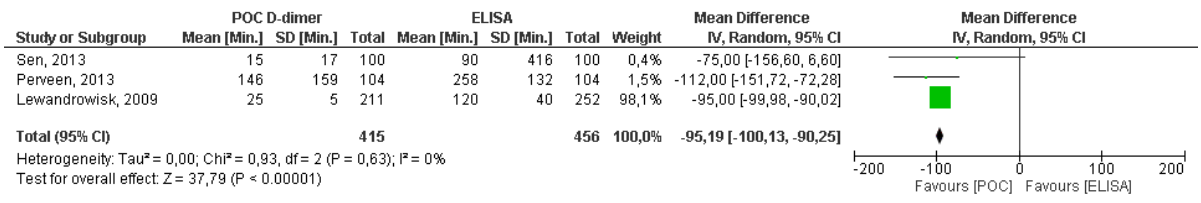


Note: Analysis using the difference between the means with a confidence interval of eight prospective and retrospective observational studies. As the rhombus does not include the corresponding vertical line, the nullity of the effect (zero) means that, in this comparison, the difference between the means was statistically significant, and as the I^2 was 99%, then the meta-analysis does not reject the hypothesis of heterogeneity.

Exam return time

The time between ordering the exam and delivering the results was short enough on all POC assay analyzers analyzed to meet the one-hour laboratory criterion set out in international POC assay standards. The combination of the estimates in the meta-analysis for the outcome turnaround time of the exam result was favorable to the POC analyzers. The time to obtain the test result using POC analyzers for D-dimer is at least 90 minutes less than in the ELISA test (Figure 6).

Figure 6. Forest Plot of the meta-analysis of the combination of negative predictive value estimates from POC tests compared to ELISA. Rio de Janeiro, RJ, Brazil, 2020



Note: Analysis by means of difference between the means with confidence interval of three prospective and retrospective observational studies. As the rhombus does not include the vertical line corresponding to the nullity of the effect (zero) it means that in this comparison the difference between the means was statistically significant, and as the I^2 was 0%, then the meta-analysis rejects the hypothesis of heterogeneity.

The POC tests were shown to be fast for determining the D-dimer with analytical performance comparable to the tests performed on central laboratory analyzers. It is important to note that almost all quantitative tests require some type of analyzer, which needs to be maintained and checked for quality.

Usability and costs

The results showed that the POC analyzers are easy to execute and the interpretation of results is simplified, since professional training is basic. The simplest test to use was Simplify®, which used a whole blood sample taken from a finger prick.

Although POC D-dimer tests may be slightly less sensitive than laboratory-based tests, the evidence suggests that they can limit the burden and additional costs associated with referrals and performing additional tests, such as CT scans or compression ultrasounds that can reduce costs and improve clinical outcomes.

The additional costs due to investments in analyzers, controls and maintenance will depend on the number of tests performed per year. The costs will be higher the lower the test volumes demanded in the service.

Quality of evidence

Evaluation of the quality of the evidence was performed by outcome considering the set of evidence from the included studies and was determined using the GRADE system, from which the quality of the evidence was considered low (Appendix).

Discussion

The pandemic caused by the new SARS-CoV-2 coronavirus spread rapidly, causing many deaths, and putting pressure on health systems worldwide, especially in view of the need to incorporate health technologies aimed not only at the diagnosis and treatment of the disease, but also management of its complications also.

Between the second half of August and the beginning of September 2020, a second wave of new cases of infection caused by SARS-CoV-2 began to be reported in some European countries, particularly in the United Kingdom, which is serving as a warning. to other countries, including Brazil, which in the same period began to show signs of stabilization of the infection and death curves caused by the disease, causing field hospitals to be deactivated in many states and municipalities.

Particularly in patients who develop the severe form of the disease and who develop severe pneumonia, the development of abnormalities in the blood clotting system is being frequently reported in the literature and reaffirming the relevance of D-dimer dosage as a supporting strategy for the risk stratification of patients, for whom high values are associated with poor prognosis and high mortality rate[28].

D-dimer is a product of fibrin degradation and its quantification has been considered especially useful in the laboratory evaluation of several situations that present with hemostasis disorders such as venous thrombosis, pulmonary thromboembolism, sepsis, in addition to several others, including infection by new coronavirus.

In an attempt to reduce the time taken to return the results of D-dimer dosing tests to remove suspicions of VTE (DVT or EP) or ICD in critically ill patients with COVID-19, the use of POC analyzers is an alternative that can be clinically useful in units where, as well as in emergency rooms, the time to make clinical decisions can impact outcomes, or those where access to tests performed in central laboratories or imaging tests can be difficult, as in primary care units[29,30].

In view of the severity of the disease and the possibility of a second wave of infections in Brazil, the need to obtain reliable results from D-dimer tests with good sensitivity rates and negative and short-term predictive value has become urgent for, with accuracy and quickly, to rule out cases of complications related to hemostasis disorders and thereby establish priorities and the best possible therapeutic approaches, which can be a differential, considering the expected increase in demand in view of the imminent possibility of a second wave in the country.

Evidence suggests that performing D-dimer tests at the point of care, combined with pre-test probability scores (Wells scale), can be a quick and safe way to discard PTE and improve patient experience in healthcare services.

The best result in average percentage of sensitivity of the analyzed tests was 98.4% and for the negative predictive value, 99.2%. Best time (shortest response time) observed using POC was 14 minutes. The joint analysis of the results of the studies revealed that, with the use of the POC, it is possible to shorten the time to access the test result by at least 95 minutes (DM = -95.19 min; 95% CI -100.13 to -90, 25; I2 = 0%, p = 0.63).

As expected, the POC analyzers showed, on average, less sensitivity and less negative predictive value than the ELISA test, which can be greater than 99%. In the joint analysis of the results of the studies, the sensitivity and the NPV of the POC analyzers were, respectively, 5.28 and 2.83 percentage points lower than those observed in the ELISA .

Quantitative tests are more accurate and, therefore, possibly more useful in clinical practice to rule out the diagnosis of PTE. It should be noted that in some POC analyzers it is also possible to quantify a range of biomarkers, so they could be used for a range of tests normally performed in these services, especially in patients with

suspected acute coronary syndrome or sepsis. restricting only to the dosage of D-dimer. In this sense, it is possible that, when effectively use, POC analyzers can in fact constitute a legacy left by the managers who opted for their incorporation in this pandemic period that we are going through in the country[31].

Regarding the POC analyzers available in Brazil, it is worth highlighting some of their main advantages and disadvantages. An advantage of the POC Pathfast® and AQT90 FLEX® analyzers is the ability to use a variety of sample specimens, including whole blood and plasma, in citrate or heparin, thus eliminating the need for sample centrifugation to analyze different analytes.

Pathfast® has the advantage of being equipped with a barcode reader, which can speed up and make the process more secure and can analyze up to six samples or parameters per run, from a single whole blood sample. However, the analysis of only 6 more analytes besides D-dimer is limited, including troponin I, NTproBNP, PCR, myoglobin, HCG and CKMB.

The main advantage of the Stratus CS® analyzer is that it offers one of the shortest turnaround times for the D-dimer test (14 minutes), but with the disadvantage in relation to the AQT 90 FLEX relative to the limited number of analytes that can be measured by the POC. In addition to the D-dimer, the analyzer can measure troponin I, PCR, NT-proBNP, myoglobin, CKMB and ßhCG, like what happens with Pathfast®.

The AQT90 FLEX® has the advantage of using the Europio marker, which allows greater Stoke deviation in relation to the fluorophore marker that is commonly used, providing the analyzer with a wavelength of the emitted light greater than that of the light used for excitation (200 to 300 nm), ensuring greater precision in the analysis of nine different analytes in addition to the D-dimer, being the only POC analyzer available in the country capable of measuring troponins I and II and procalcitonin, in addition to the other analytes analyzed by the other POCs. Its disadvantage in relation to the NycoCard, and the same occurs with Pathfast®, are its physical dimensions, much larger.

The main advantage of NycoCard® is its portability. The analyzer has the following dimensions: 200x170x70 mm and weighs only 540g, including the reading pen and batteries. However, its disadvantage in relation to AQT 90 FLEX® is the limitation of analytes that can be measured by the analyzer, being limited to PCR, HbA1c, D-Dimero and µ-Albumin and its precision.

Therefore, the AQT 90 FLEX® and Pathfast® seem more useful than NycoCard®, considering the different analysis possibilities for different analytes, although in terms of portability the NycoCard® may be more useful. VIDAS® cannot be considered a POC assay because in it, the sample needs to be centrifuged before testing.

Two studies evaluated the costs and consequences of using POC for D-dimer measurement. In all of them, the POC resulted in comparable health outcomes (QALY), although there were exceedingly small differences, which is why the authors opted for the cost-minimization analysis, demonstrating that, although they are slightly less sensitive than the D tests. - lab-based dimers, they can limit the burden and additional costs associated with additional test routings and conduct, with a reduction in the delivery time of the test results, which was reflected in the reduction of residence times and decision-making clinical decisions.

The methodological quality of the studies analyzed was moderate; most were well designed but were not randomized or blind. The number of point-of-care D-dimer tests analyzed or compared in each study was small, using different cutoff points and some studies used accuracy as the primary outcome measure for performance analysis, which should be considered as study limitation. The results seem reliable and reproducible with internal validity, but they can be different if applied to larger populations and between different profiles of health professionals, which reduces the external validity and, consequently, the power to extrapolate the results, especially regarding costs, for Brazilian reality.

Conclusion

The profile of the patients evaluated in the studies, different from the real world, in this case, patients infected by COVID-19 and the absence of studies developed in Brazil in the review should be considered as limitations of the study, even though the purpose of the review was to assess the utility clinical use of POC D-dimer analyzers to rule out the diagnosis of PTE and not COVID-19. However, it should be considered that, as it is a technology that in the country is still in the initial diffusion phase, therefore, even at the beginning of its life cycle curve, it is reasonable that there are no studies developed in the country yet.

Based on the above, the study showed that there is scientific evidence to suggest that the use of POC analyzers for D-dimer measurement has clinical utility to rule out cases of VTE (TEP and EP) CID in patients diagnosed with COVID-19 seen in the emergency room or in primary care units, as a complement to risk stratification by the Wells scale, classified in the nucleus ≤ 4 on the scale.

The analyzers, in addition to allowing less time for the return of the test result, which can be done at the service site and by non-specialized personnel, are also capable of measuring other biomarkers, in particular, PCR, troponins I and II and procalcitonin, very useful in the daily care of patients with acute myocardial infarction and patients with bacterial infections, including sepsis, so that a legacy of the incorporation of this technology can be guaranteed after the pandemic of COVID-19.

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Appendix

Search strategies used in the researched databases.

Medline (213)	((("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields]) AND ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("embolism"[All Fields] AND "pulmonary"[All Fields]) OR "embolism pulmonary"[All Fields])) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("embolisms"[All Fields] AND "pulmonary"[All Fields]) OR "embolisms pulmonary"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("pulmonary"[All Fields] AND "thromboembolisms"[All Fields]) OR "pulmonary thromboembolisms"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("pulmonary"[All Fields] AND "thromboembolism"[All Fields]) OR "pulmonary thromboembolism"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("thromboembolism"[All Fields] AND "pulmonary"[All Fields]) OR "thromboembolism pulmonary"[All Fields]) OR (("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields] OR ("thromboembolisms"[All Fields] AND "pulmonary"[All Fields]) OR "thromboembolisms pulmonary"[All Fields]) AND ("point of care systems"[MeSH Terms] OR ("point of care"[All Fields] AND "systems"[All Fields]) OR "point of care systems"[All Fields] OR ("point"[All Fields] AND "care"[All Fields] AND "systems"[All Fields]) OR "point of care systems"[All Fields])) OR ("point of care systems"[MeSH Terms] OR ("point of care"[All Fields] AND "systems"[All Fields]) OR "point of care systems"[All Fields] OR ("point"[All Fields] AND "care"[All Fields] AND "technology"[All Fields]) OR "point of care technology"[All Fields]) OR (("point of care systems"[MeSH Terms] OR ("point of care"[All Fields] AND "systems"[All Fields]) OR "point of care systems"[All Fields] OR ("point"[All Fields] AND "care"[All Fields]) OR "point of care"[All Fields]) AND ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("enzyme"[All Fields] AND "linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields])) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("assay"[All Fields] AND "enzyme"[All Fields] AND "linked"[All Fields] AND "immunosorbent"[All Fields]) OR "assay enzyme linked immunosorbent"[All Fields]) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("assays"[All Fields] AND "enzyme"[All Fields] AND "linked"[All Fields] AND "immunosorbent"[All Fields]) OR "assays enzyme linked immunosorbent"[All Fields]) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("enzyme"[All Fields] AND "linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields]) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("enzyme"[All Fields] AND "linked"[All Fields] AND "immunosorbent"[All Fields] AND "assays"[All Fields]) OR "enzyme linked immunosorbent assays"[All Fields]) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("immunosorbent"[All Fields] AND "assay"[All Fields] AND "enzyme"[All Fields] AND "linked"[All Fields]) OR "immunosorbent assay enzyme linked"[All Fields]) OR ("enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR ("immunosorbent"[All Fields] AND "assays"[All Fields] AND "enzyme"[All Fields] AND "linked"[All Fields])

	OR "immunosorbent assays enzyme linked"[All Fields]) OR ("elisa s"[All Fields] OR "elisas"[All Fields] OR "enzyme linked immunosorbent assay"[MeSH Terms] OR ("enzyme linked"[All Fields] AND "immunosorbent"[All Fields] AND "assay"[All Fields]) OR "enzyme linked immunosorbent assay"[All Fields] OR "elisa"[All Fields])) AND "d dimer"[All Fields]
Embase (6)	(((lung AND embolism OR thromboembolism OR venous) AND thromboembolism OR deep) AND vein AND thrombosis AND point AND of AND care AND testing OR d) AND immunoassay AND enzyme AND linked AND immunosorbent AND assay AND d AND dimer AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [humans]/lim AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [review]/lim)
Cochrane (6)	#1- Pulmonary Embolism or Embolism, Pulmonary or Embolisms, Pulmonary or Pulmonary Thromboembolisms or Pulmonary Thromboembolism or Thromboembolism, Pulmonary or Thromboembolisms, Pulmonary (4555 docs) #2- Enzyme-Linked Immunosorbent Assay or Assay, Enzyme-Linked Immunosorbent or Assays, Enzyme-Linked Immunosorbent or Enzyme Linked Immunosorbent Assay or Enzyme-Linked Immunosorbent Assays or Immunosorbent Assay, Enzyme-Linked or Immunosorbent Assays, Enzyme-Linked or ELISA (13337 docs) #3- Point-of-Care Systems or Point of Care Technology or Point-of-Care (4011 docs) #4- D dmer (1937 docs); #5- #1 and #2 and #3 and #4
BVS (6)	(tw:(Embolia Pulmonar or Tromboembolia Pulmonar or Tromboembolismo Pulmonar or Tromboembolia Venosa or Tromboembolia)) AND (tw:(Sistemas Automatizados de Assistência Junto ao Leito or Tecnologia de Assistência Junto ao Leito)) AND (tw:(Ensaio de Imunoadsorção Enzimática or ELISA or Ensaio Imunoadsorvente Enzima-Associado or Ensaio Imunoadsorvente Ligado à Enzima or Ensaio de Imunoadsorção Ligado à Enzima))
ECRI (1)	Point-of-Care D dimer Assay or POC D dimer assay
CAPES (30)	“d-dimero”
Google (86)	"d dimer assay" and "Thromboembolism, Pulmonary"

Brands and models of POC analyzers evaluated in the studies included in the review.

Brands / Models	**Test / Sample Principle**	**Manufacturer**	**ANVISA Registration**
Cardiac®	Monoclonal antibody / whole blood	Roche	No
Alere Triage®	Fluorescence / blood / plasma	Biosite	No
Nycocard®	Sandwich / plasma method	Nycomed Pharma	25351667977/2013-31
Simplify®	Immunochromatography / blood / plasma	Inverness Medical	No
AQT 90 FLEX®	Immunofluorescence / Europium / blood / plasma	Radiometer	25351589718/2008-49
SimpliRed®	Agglutination / Qualitative / blood	AGEN Biomedical	No
Stratus CS®	Sandwich / blood / plasma method	Siemens	25351725689/2013-94
Mini VIDAS®	Sandwich / plasma method	Bio-Mériex	No
PATHFAST®	Enzyme immunoassay / blood / plasma	Mitsubishi	25351126161/2009-24
Hipro AFS/1®	Immunoturbidimetric / sodium citrate	Hipro Biotechnology	No
Standard F200®	Lateral flow / plasma immunoassay	SD Biosensor	No
iChroma-II®	Lateral flow / plasma immunoassay	Boditech Med	No
AFIAS-1®	Lateral flow / plasma immunoassay	Boditec Med	No
Nano-Checker 710®	Immunochromatography / blood / plasma	Nano-Ditech	No

Summary of results of the evaluation of the quality of evidence GRADE)

Certainty assessment							Sumário de Resultados				
							Taxas de eventos do estudo (%)			Efeitos absolutos potenciais	
Participantes (estudos) Seguimento	Risco de viés	Inconsistência	Evidência indireta	Imprecisão	Viés de publicação	Overall certainty of evidence	Com ensaios ensaios imunoenzimáticos	Com Ensaios D-dímero point-of-care	Efeito relativo (95% CI)	Risco com ensaios ensaios imunoenzimáticos	Diferença de risco com Ensaios D-dímero point-of-care
Sensibilidade (seguimento: média 1 semanas; avaliado com: Percentual de Sensibilidade)[a]											
6590 (8 estudos observacionais)	grave [b]	não grave	não grave	grave [c]	nenhum	⊕⊕◯◯ BAIXA	3315	3275	-	A média sensibilidade foi **0.95** %	DM **0.07** % **mais** (0.19 mais para 0.01 mais)
Usabilidade (seguimento: média 1 semana; avaliado como: Facilidade de uso)[e]											
62 (3 estudos observacionais)	grave [b]	não grave	grave [e]	não grave [e]	nenhum	⊕⊕◯◯ BAIXA	A diversidade dos estudos recuperados e as técnicas e desfechos utilizadas para avaliar a usabilidade em termos de facilidade de uso dificulta fazer comparações diretas.				
Tempo de Retorno (seguimento: média 1 dia; avaliado como: Tempo para a entrega do resultado)											
1332 (3 estudos observacionais)	grave [b]	não grave	não grave	grave [f]	nenhum	⊕⊕◯◯ BAIXA	666	666	-	A média tempo de Retorno foi **156** minutos	DM **94** **minutos mais alto** (72 mais alto para 335.5 mais alto)
Valor Preditivo Negativo (seguimento: média 1 mês; avaliado com: Exames negativos em doentes que de fato não tiveram a doença)											
6590 (8 estudos observacionais)	grave	grave	não grave	grave	nenhum	⊕◯◯◯ MUITO BAIXA	3315	3275	-	A média valor Preditivo Negativo foi **99.9** %	**0** % (0 para 0)

Explanation:

a. The percentage of sensitivity and negative predictive value (VPN).

b. Most cross-sectional observational studies, without a proper description of the criteria used for the selection of participants and without randomization.

c. Different designs although using the same outcome measures in most.

d. The rates, chances, or probabilities of changes in suspected diagnosis, routes and flows of patient care, time to return to the examination result and time to start definitive treatment were considered.

e. Different strategies and outcomes were used in the studies to assess usability in terms of ease of use, but non resulted and quantitative data.

f. The studies considered different criteria for measuring the return time.