

How artificial intelligence during the pandemic modified the role of a biomarker as d-dimer

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ABSTRACT

Artificial intelligence (AI) was introduced in medicine to make some difficult decision-making regarding diagnostics and/or treatments easy. Its application derives from the improvement of information obtained with computer sciences and informatics, in particular with information derived by algorithms obtained with special informatics support as machine learning. The scenario of hospital changes induced by the COVID-19 pandemic makes easy the application of AI for some clinical updates. Being lung failure with pulmonary embolism is the most common cause of death for inpatients with COVID-19, some biomarkers such as the d-dimer are constantly used associated with other clinical features in order to improve medical assistance. For this reason, d-dimer during the pandemic changed its traditional use for predictive negative value in patients with suspected pulmonary embolism and took relevance for its values giving the chance to change the intensity of anticoagulation for several inpatients. In most cases, according to data reported from several cohorts, these changes improved the morbidity and mortality of a significant percentage of inpatients with COVID-19. The International medical prevention registry on venous thromboembolism and d-dimer and modified sepsis-induced coagulopathy scores were the most used scores derived from AI and dedicated

to these clinical aspects in inpatients with COVID-19. Therefore, this review was dedicated to flexible changes that we can use after d-dimer values in different clinical scenarios that vary from disseminated intravascular coagulation to pulmonary embolism to COVID-19.

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Introduction

Artificial intelligence (AI) was introduced in medicine to render easy some difficult decision-making regarding diagnostics and/or treatments. Its application derives from the improvement of information obtained with computer sciences and informatics, in particular with information derived by algorithms obtained with special informatics support as machine learning.¹ The challenges that the COVID-19 pandemic created for many health systems also led many healthcare organizations around the world to start some decision-making according to AI support and because the first waves of diseases were characterized by increased morbidity and mortality for lung failure with pulmonary embolism, some biomarker as d-dimer took considerable relevance in daily clinical practice.² D-dimer is a product of fibrin degradation released during processes involved in thrombus formation and degradation.³ For this reason, in daily clinical practice it is used as a biomarker mainly in suspected venous thromboembolism (VTE) or disseminated intravascular coagulation (DIC).^{4,5}

Yet, its increase has been found during several other conditions as cancer, thrombophilia, chronic inflammatory diseases, pregnancy, recent surgery, prolonged hy-

promobility, other acute cardiovascular events, COVID-19, and so on.⁶⁻¹²

In daily clinical practice, d-dimer is a biomarker with consolidated experiences from a diagnostic and a prognostic point of view. Its daily use in VTE management is associated with its predictive negative value,¹³ while its positive value is included in International Society on Thrombosis and Haemostasis criteria to diagnose DIC.¹⁴ However, values of d-dimer may assume a prognostic role in case of confirmed VTE, in particular pulmonary embolism (PE) according to data from real-life registries such as the RIETE registry.¹⁵

In truth, this double ability of d-dimer as a biomarker that may be utilized both in case of increased or decreased value may induce some confusion in the daily clinical management of patients. In particular, patients that show an increased value of d-dimer but without an objective diagnosis of VTE or DIC have usually a twisty clinical course also from a therapeutic point of view.

Yet, in recent years, increased values of d-dimer have also been used as biomarkers of COVID-19 at increased risk of developing severe complications such as lung failure, massive PE, and death for any reason.¹²

In the next paragraphs, we summarized all useful diseases in which d-dimer values may be considered for clinical management including positive values, negative values, and predictive negative values.

Disseminated intravascular coagulation and other hyperfibrinolytic conditions

Being a fibrin degradation product, all conditions associated with primary or secondary hyperfibrinolysis are associated with increased levels of d-dimer.¹⁶ Therefore, inherited conditions associated with hyperactivation of fibrinolysis as deficiency of alpha2 antiplasmin or other protease inhibitors that may lead to hyperactivation of plasmin may be associated with increased d-dimer levels.¹⁷

In the same way, several acquired conditions associated with hyperfibrinolysis and increased d-dimer levels are known. First, drugs that can generate hyperfibrinolysis as fibrinolytic drugs may also induce increased levels of d-dimer.¹⁸

Of course, there are several medical illnesses that are associated with primary or secondary hyperfibrinolysis that may lead to DIC.¹⁹ The most known disease associated with hyperfibrinolysis is liver cirrhosis.²⁰ Patients with liver cirrhosis in fact may show frequent complications associated with hyperfibrinolysis as haematomas or major bleedings.²⁰

Other relevant diseases that may be associated with secondary induced hyperfibrinolysis leading to DIC are mainly infectious diseases in particular sepsis or hematological malignancies.^{21,22} DIC may be identified ac-

ording to international criteria and guidelines and may recognize several, and different clinical phases. In all phases, laboratory biomarkers such as the increase of d-dimer and the decrease of fibrinogen and platelets are usually present.^{23,23} Therefore, d-dimer remains a biomarker with a diagnostic role in the diagnosis of VTE and DIC and it may be useful during treatments of VTE and DIC when associated with severe medical illnesses such as sepsis or hematological malignancies.

Increased d-dimer values and their interpretation

D-dimer is a biomarker mainly used in differential diagnosis for VTE for its predictive negative value.

Yet, this main use is related to the possible increase of d-dimer during other clinical conditions that may induce misunderstanding in clinical practice.

First, aging is associated with increased d-dimer levels.²⁵ An aged-adjusted value in these cases may be useful when increased levels of d-dimer are present and the risk of PE is still present.²⁶

Active cancer, in fact, has been associated with increased values of d-dimer.²⁷ Some articles speculate about a prognostic role of d-dimer in this clinical setting or in its association with new onset of cancer or the presence of oligo symptomatic cancer-associated thrombosis.^{27,28} Furthermore, the use of antineoplastic drugs may be associated with increased values of d-dimer as far as the placement of long-term venous lines (*e.g.*, port a cath or others).^{29,30}

Similarly, other chronic inflammatory diseases have been associated with increased d-dimer levels.⁸ In addition, in this case, d-dimer values have been associated with the prognostic evolution of inflammatory disease *per se*.³¹

Cardiovascular diseases, with acute or chronic clinical presentation are frequently associated with increased d-dimer (*e.g.*, acute myocardial infarction, aortic dissection, atrial fibrillation, and so on).³²⁻³³

Furthermore, also physiological conditions such as pregnancy are associated with a physiological hypercoagulable state with increased values of d-dimer and fibrinogen.³⁴ These abnormalities do not influence prognostic outcomes of pregnancy according to several studies.³⁵

Finally, physiological abnormalities of clotting power in asymptomatic thrombophilic carriers may be associated with increased d-dimer without acute diseases.³⁶

D-dimer in venous thromboembolism

D-dimer can be easily tested in an emergency for the differential diagnosis of venous thromboembolism

(*i.e.*, deep vein thrombosis and/or pulmonary embolism). However, several items in its daily clinical use remain unclear and frequently inappropriate testing enlarges these troubles.

Several guidelines, according to data available in the literature, underline that the use of d-dimer is useful to rule out a diagnosis of VTE.³⁷ For this reason, all experts suggest its predictive negative value in the differential diagnosis of deep vein thrombosis or pulmonary embolism.³⁷ In particular, after a clinical evaluation with or without associated diagnostic scores such as Wells Score and so on, patients that show low values of d-dimer did not suffer from any type of VTE.³⁸

In emergency enzyme-linked immunosorbent, assay determination has the highest accuracy; immunoturbidimetric assay seems the most suitable on an emergency basis because of its rapid performance.³⁹

Yet, according to the possible presence of several comorbidities or clinical conditions that may be associated with increased d-dimer levels, also imaging to rule out definitively DVT or PE is frequently required.³⁷

On the other hand, although the predictive negative role of d-dimer in the differential diagnosis of VTE is useful, a prognostic role of d-dimer in patients with overt and objectively diagnosed VTE is present.^{15,40,41} In these studies, a d-dimer value over 95th percentile was testified to have a worse prognostic role at 30 and 90 days after VTE diagnosis.

D-dimer and COVID-19

Since the beginning of the COVID-19 outbreak, an associated hypercoagulable state has been demonstrated in inpatients with an aggressive course of the disease (*e.g.*, inpatients in intensive care unit).⁴² Therefore, associated with a hypercoagulable state in patients affected by COVID-19 also an increased rate of venous thromboembolism has been detected.⁴³ For this reason, patients with elevated levels of d-dimer were frequently addressed to diagnostics to detect VTE routinely in this clinical scenario. However, because at the beginning of the outbreak, it was difficult to address all patients to diagnostics for VTE, several guidelines have been addressed on this topic in order to simplify the management of infected patients. In all guidelines, all scientific societies suggested pharmacological thromboprophylaxis in inpatients with COVID-19.⁴⁴ Yet, because the prognosis of patients with more elevated values of d-dimer was worse than those with lower levels and because patients treated with all types of anticoagulants during COVID-19 seemed to have a better prognosis, several clinical scores included d-dimer values to stratify prognosis of inpatients with COVID-19. The most used scores were the International medical prevention registry on venous thromboembolism and d-dimer score and the sepsis-induced coagulopathy score.^{45,46} These

scores in the presence of 2-3 fold increase of d-dimer values suggested therapeutic doses of low molecular weight heparin in order to reduce mortality for PE in inpatients with COVID-19.⁴⁷

Because of the associated increased mortality for lung failure associated with PE, in the first waves of the pandemic these options (*i.e.*, to treat with therapeutic doses of LMWH patients with 3 fold increase of d-dimer), were frequently adopted although an increase of bleeding events was detected too in this cohort of patients.^{48,49}

D-dimer values and risk of recurrent venous thromboembolism after withdrawal of anticoagulation

After an objectively diagnosed VTE, pharmacological anticoagulation, when not contraindicated, is suggested for 3-6-12 months or rarely indefinitely. However, when anticoagulation is stopped d-dimer testing is suggested in order to understand the risk of recurrent VTE: patients that show increased d-dimer values, in fact, have an increased risk of VTE recurrence.⁵⁰

This association does not influence the site of recurrence and it is not influenced by the severity of the first event but maybe it depends only on the presence of underlying persistent prothrombotic factors.

Discussion and Conclusions

Several open issues are present on the use of d-dimer although its testing has been used for several years. Its use has been modified by recent advances in AI.

Based on what we reported the main trouble that we discuss daily in the clinical management of inpatients or outpatients is about appropriate testing of d-dimer. This can be possible because d-dimer is a biomarker that can be used in case of positive or negative results.

The predictive negative value of d-dimer suggested in international guidelines to exclude VTE is the most reliable use of d-dimer testing in clinical practice. Yet, in case of positive values, its use may have relevant implications in the diagnosis and therapeutic monitoring of DIC; furthermore, increased d-dimer has also prognostic implications in case of VTE and the recent pandemic confirmed this attitude as we reported. To confirm its relevant role in case of a strong increase of d-dimer values, several scores during the pandemic have been used with great impact not only in clinical utility but also related to improved prognosis of patients affected by COVID-19.

AI, in fact, has been applied using d-dimer values after that its utility was testified by algorithms derived

by several cohorts of patients affected by COVID-19.

This way, several misunderstandings of underlying conditions that may alter d-dimer levels should be excluded, because artificial intelligence and derived scores confirmed the utility of d-dimer testing also to choose the appropriate therapeutic approach (*e.g.*, intensity of enoxaparin doses in inpatients with COVID-19).

This new approach is one of different chances of any daily testing modified by the use of artificial intelligence. After the good experience during the pandemic, further confirms are needed in other daily clinical conditions in which hypercoagulable state and its management could be associated with different prognoses.

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