# PEMANFAATN TES D-DIMER PADA LABORATORIUM DAN PRAKTEK KLINIS

Oleh

Dr. dr. Rikarni, Sp.PK (K)

Karya Ilmiah disajikan dalam Seminar

Simposium PDS PatKLIn Wilayah Sumatera Barat 2022

"D-Dimer dan Prostate Specific Antigen"

Padang, 18 Desember 2022

**PERHIMPUNAN DOKTER SPESIALIS PATOLOGI KLINIK DAN KEDOKTERAN LABORATORIUM INDONESIA**
**CABANG PADANG**
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Padang, 30 November 2022

Kepada, Yth :
Ibu DR. Dr. Rikarni, Sp.PK (K)
di Tempat

Bersama ini kami memohon kesediannya sebagai Narasumber pada Symposium Perhimpunan Dokter Spesialis Patologi Klinik dan Kedokteran Laboratorium Indonesia (PDS PatKLIn) Cabang Padang, untuk menghadiri Seminar dengan Tema : "**D-Dimer dan PSA** : *Aspek Klinis dan Laboratorium untuk Optimalisasi Diagnostik dan Tatalaksana*" dan Pergantian Pengurus PDS Patklin Cabang Padang, yang dilaksanakan pada :

| | |
|---|---|
| Hari/Tanggal | : Minggu/ 18 Desember 2022 |
| Waktu | : 08.00 – 12.00 WIB |
| Tempat | : Aula Prof. M. Syaaf, FK Unand Kampus Jati |

Demikian disampaikan, atas kehadiran Bapak/Ibu, kami ucapkan terima kasih.

Ketua PDS Patologi Klinik dan Kedokteran Laboratorium Cabang Padang

Dr. dr. Efrida, Sp.PK (K), M.Kes
NA PK. 02-2012- 05

# SERTIFIKAT

diberikan kepada

## Dr. dr. Rikarni, Sp. PK (K)

sebagai

Pembicara

Atas Partisipasinya dalam kegiatan

**Simposium PDS Patklin Wilayah Sumatera Barat 2022**
**D-Dimer dan Prostate Specific Antigen**

SKP IDI No : 2057/IDI-WIL-SB/SK/XII/2022
Pembicara: 8 SKP
Peserta: 2 SKP
Moderator: 1 SKP
Panitia: 1 SKP

**Dr. dr. Efrida, Sp.PK (K), M. Kes**
Ketua PDS Patklin
Wilayah Sumbar

**Marcel Aditiawarman**
General Business
Manager PT EMP

# PEMANFAATAN TES D-DIMER PADA LABORATORIUM DAN PRAKTEK KLINIS




D-dimer atau fragmen D-dimer *(fibrin degradation fragment)* adalah suatu jenis uji sampel darah di laboratorium yang bertujuan untuk membantu klinisi dalam diagnosis penyakit dan kondisi yang menyebabkan hiperkoagulabilitas, suatu kecenderungan darah untuk membeku melebihi ukuran normal.

Uji D-dimer juga dipakai untuk membantu melakukan diagnosis DIC *(Disseminated Intravascular Coagulation)*, kondisi akut yang kompleks yang dapat timbul dari berbagai situasi seperti beberapa prosedur pembedahan, gigitan ular berbisa, penyakit hati dan kondisi setelah melahirkan.

D-dimer sendiri merupakan fragmen protein yang dibuat tubuh ketika gumpalan darah larut dalam tubuh. Normalnya, D-dimer berjumlah kurang dari 500 nanograms per milliliter (ng/mL). Bila hasil pemeriksaan normal D-dimer lebih dari batas normal, hal tersebut menunjukkan bahwa pasien memiliki kondisi gangguan pembekuan darah. Meski pemeriksaan ini tidak bisa mengungkapkan jenis kondisi pembekuan yang dialami atau lokasi gumpalan berada, pemeriksaan D-dimer sering digunakan untuk menegakkan diagnosis penyakit tertentu.

Berikut adalah link *Google Drive* pemaparan materi yang disampaikan Dr. dr. Rikarni, Sp. PK (K) pada Simposium Perhimpunan Dokter Spesialis Patologi Klinik dan Kedokteran Laboratorium Indonesia (PDS PatKLin) cabang Padang yang berjudul :

**PEMANFAATAN TES D-DIMER PADA LABORATORIUM DAN PRAKTEK KLINIS**

Pada Minggu, 18 Desember 2022

# PEMANFAATAN TES D-DIMER PADA LABORATORIUM DAN PRAKTEK KLINIS

**Rikarni**

## PENDAHULUAN

D-dimer telah menjadi salah satu tes koagulasi yang sering diminta. Pemeriksaan D-dimer yang tepat memainkan peran penting dalam diagnostic proses gangguan koagulasi sistemik, terutama koagulasi intravascular diseminata dalam hubungannya dengan tes koagulasi lainnya. Trombosis arteri dan vena adalah penyebab paling umum dari kematian diseluruh dunia. Meski faktor risiko klinis sudah diketahui dengan baik dan telah diidentifikasi, perlu ditemukan pemeriksaan laboratorium yang mudah dan sederhana yang dapat menyampaikan informasi tentang proses koagulasi yang sedang berlangsung. Penguraian mendetail dari proses fibrinolitik seiring dengan munculnya antibody monoclonal. Ilmu pengetahuan dan teknologi membuka jalan untuk identifikasi D-dimer sebagai biomarker aktivasi koagulasi dan pembentukan thrombus. [1]

## D-DIMER

D-dimer merupakan *cross-linked fibrin degradation product* dari hasil pemecahan fibrin. Metode yang sering dipakai adalah metode aglitunasi latex untuk mendeteksi *cross linked* fibrin D-dimer. Pembentukan D-dimer diilustrasikan pada Gambar 3 dan Gambar 4. Trombin mengubah fibrinogen untuk monomer fibrin yang terdiri dari domain -E pusat dan 2 domain-D peripheral. Dengan demikian, monomer fibrin berpolimerisasi secara spontan membentuk jaringan fibrin yang tidak stabil. Faktor XIII, diaktifkan oleh trombin, lalu ikatan silang domain-D monomer fibrin yang berdekatan, yang memperkuat fibrin. Plasmin yang terikat fibrin mendegradasi jaringan fibrin menjadi fragmen yang larut : D-dimer dan fragmen E. Kadar D-dimer plasma mencerminkan luasnya koagulasi dan aktivasi fibrinolysis dan keadaan hiperkoagulasi yang meningkat [2,3]

tiga jenis yang umum: Enzyme Linked Immunosorbent Assays (ELISA), uji imunofluoresen, dan uji aglutinasi lateks. [3]

Tes berbasis ELISA menggunakan kemampuan antibodi monoklonal yang berada di permukaan tabung atau pelat untuk menangkap Antigen D-dimer. Prinsip, plasma diinkubasi di dalam tabung atau piring sampai antibodi mengikat ke D-dimer. Setelah dicuci, antibodi monoklonal kedua terhadap D-dimer yang ditandai dengan enzim terlekat ditambahkan.Setelah pencucian , sinyal dikembangkan menggunakan substrat enzim. Densitas optikal atau sinyal yang dipancarkan oleh tehnik chemiluminescence kemudian diukur, yang proporsional dengan jumlah D-dimer yang ada dalam plasma pasien. Lebih cepat dan lengkap metode ELISA otomatis memiliki antibodi penangkap yang dilapisi pada ujungnya dan reagen dalam strip.[1]

Pengujian aglutinasi didasarkan pada partikel lateks atau polistiren yang membawa antibodi monoklonal. Pengikatan Antigen D-dimer dalam plasma yang ditambahkan ke partikel ini akan menyebabkan aglutinasi partikel, yang dapat dibaca dengan menggunakan yang berbeda

teknik. Metode aglutinasi semikuantitatif mungkin memimpin

**APLIKASI KLINIS PEMERIKSAAN D-DIMER**

Pengujian D-dimer telah membuktikan perannya secara meyakinkan pada tromboemboli vena. Internasional Society of Thrombosis and Haemostasis (ISTH) juga mendukung peran pemeriksaan D-dimer dalam algoritma diagnostik untuk Disseminated Intravascular Coagulation (DIC). Baru-baru ini, potensi lainnya aplikasi pemeriksaan D-dimer telah diakui (antara lain akut diseksi aorta, trombosis akses vaskular, infeksi berat, dan sepsis); namun, sejalan dengan kemajuan dalam pemanfaatan, aplikasi klinis untuk pemeriksaan D-Dimer dapat dilihat pada tabel 1. [1]

Tabel 1. Aplikasi Klinis untuk D-Dimer [1]

Tabel 1. Aplikasi Klinis untuk D-Dimer [1]

| |
|---|
| • Excluding venous thromboembolism in patients with ***low*** clinical probability for venous thromboembolism by clinical prediction scores |
| • Establishing the risk of recurrent thrombosis; thus aiding in the decision-making process of required duration of anticoagulation for patients with venous thromboembolism |
| • Diagnosis and management of disseminated intravascular coagulation |
| • Excluding acute aortic dissection |
| • Predicting and monitoring thrombotic complications in patients with severe infections and sepsis |
| • *Detection of thrombotic risk in malignancies, and with the use of chemotherapy and growth factor drugs (e.g., erythropoietin)* |
| • *Vaso-occlusive crises in sickle cell disease* |
| • *Suspicion of intracardiac thrombus in left ventricular aneurysms* |
| • *Predicting recurrent strokes in those with cardioembolic stroke* |
| • *Prognostication in peripheral artery disease* |

**Definisi *Disseminated intravascular coagulation***

Definisi konsensus dari DIC telah diusulkan : DIC adalah suatu sindrom didapat yang ditandai dengan aktivasi koagulasi intravaskular yang luas yang timbul dari beragam penyebab yang berbeda. Ini bisa berasal dari hal yang menyebabkan kerusakan pada mikrovaskular, yang jika cukup parah, dapat menimbulkan disfungsi organ.[4,5]

**Etiologi DIC**

Beberapa kelainan patologis dasar yang menyebabkan DIC diperlihatkan tabel 1.[6]

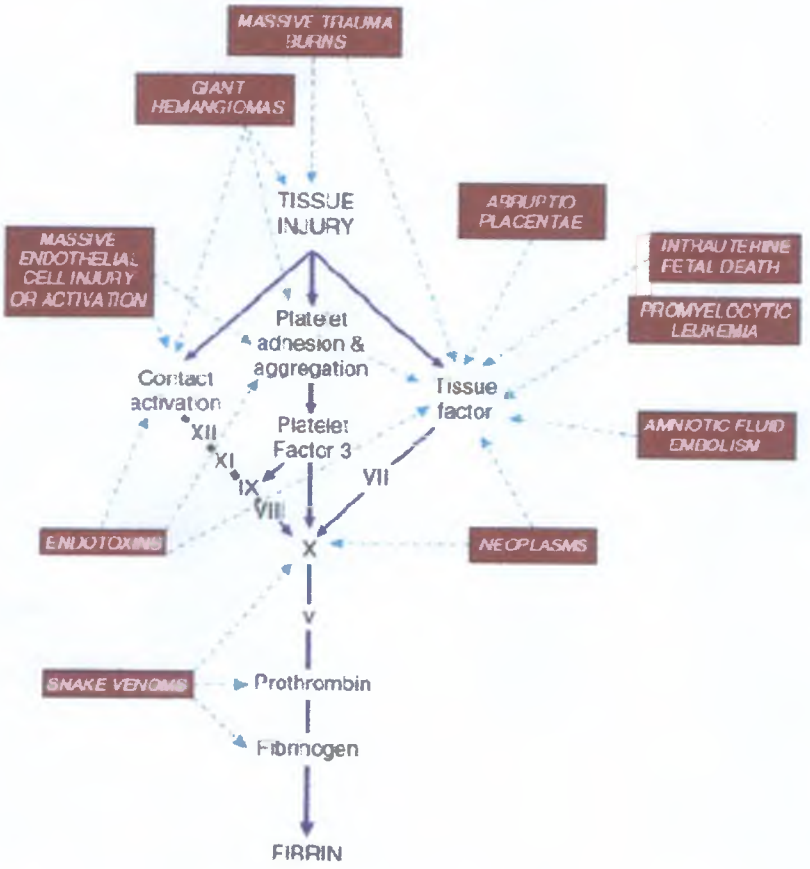
Tabel 1. Kelainan dasar yang sering menyebabkan DIC.[6]

| |
|---|
| Sepsis : |
| bakteri (staphylococcus, streptococcus, pneumococcus, meningococcus, batang gram negatifi), virus, jamur, parasit, Rickettsia |
| Trauma dan cedera jaringan |
| cedera otak, luka bakar yang luas, emboli lemak, rhabdomiolisis |
| Kelainan vaskular |
| *giant hemangiomas* (*kasabach Merritt syndrome*), aneurisma aorta |
| Komplikasi obsteterik |
| solusio plasenta, emboli amnion, sindrom kematian janin, abortus sepsis |
| Kanker |
| adenokarsinoma (prostat, pankreas), keganasan hematologi (leukemia promielositik akut) |
| Kelainan imunologi |
| Reaksi transfusi hemolitik akut, *organ or tissue transplant rejection, Graft-versus-host disease* |
| Obat |
| Agen fibrinolitik, warfarin, reaksi obat (amfetamin) |
| Bisa ular |
| Penyakit hepar |
| *Fulminant hepatic failure*, sirosis hati |
| *Shock, respiratory distress syndrome, transfusi masif* |

**Patofisiologi DIC**

Patofisiologi DIC sangat kompleks. Mekanisme yang memicu atau mengaktifkan DIC bekerja pada proses yang terlibat dalam hemostasis normal, termasuk adhesi dan agregasi trombosit, aktivasi kontak (intrinsik), dan jalur aktivasi faktor jaringan (ekstrinsik) (Gambar 3). Trombin secara persisten dihasilkan, dan fibrin terbentuk dalam sirkulasi darah. Fibrinogen, berbagai faktor koagulasi lainnya, dan trombosit dikonsumsi. Mekanisme fibrinolitik mulai diaktifkan, dan sejumlah besar FDP diproduksi, yang selanjutnya semakin merusak fungsi hemostatik. Selanjutnya, fibrinolisis dihambat. Perdarahan, syok, dan oklusi vaskular biasanya terjadi dan menimbulkan kerusakan fungsi berbagai sistem organ. Proses kompensasi normal menjadi rusak, menciptakan lingkaran setan berulang. Hasil akhir ditentukan oleh interaksi yang dinamis antara beragam proses patologis dan mekanisme kompensasi, seperti, deposisi fibrin versus fibrinolisis; deplesi versus replesi faktor koagulasi

dan trombosit; dan produksi versus pembersihan fibrin, FDPs, dan produk koagulasi lainnya (Gambar 3).[4]




Gambar 1, Mekanisme awal DIC[2]

Tabel 2. Sistem skor diagnosis untuk *disseminated intravascular coagulation.*[7]

Penilaian risiko :

Apakah pasien mempunyai kelainan dasar yang diketahui berhubungan dengan DIC?
Jika ya, lanjutkan algoritma
Jika tidak, tidak dipakai algoritma

Lakukan pemeriksaan laboratorium hitung trombosit, D-dimer, PT, Fibrinogen

Skor hasil pemeriksaan sebagai berikut :

| | | |
|---|---|---|
| Hitung trombosit | : 50.000 -100.000/$mm^3$, | nilai = 1 |
| | < 50.000/$mm^3$ | nilai = 2 |
| D-dimer | : tidak meningkat, | nilai = 0 |
| | meningkat sedang, | nilai = 2 |
| | meningkat tinggi, | nilai = 3 |
| Pemanjangan PT | : < 3 detik, | nilai = 0 |
| | 3 - < 6 detik, | nilai = 1 |
| | ≥ 6 detik, | nilai = 2 |
| Kadar Fibrinogen | : ≥ 1g/L | nilai = 0 |
| | < 1 g/L | nilai = 1 |

Hitung skor sebagai berikut :
≥ 5, sesuai dengan *overt* DIC, ulang skor setiap hari
< 5, kesan sebagai *nonovert* DIC, ulangi skor dalam 1-2 hari kemudian

*Disseminated intravascular coagulation* (DIC) merupakan sebuah diagnosis klinikopatologi yang didefinisikan oleh International Society on Thrombosis and Hemostasis (ISTH). *Disseminated intravascular coagulation* (DIC) memiliki karakteristik aktivasi koagulasi intravaskular yang terjadi karena berbagai etiologi. Kondisi DIC terjadi pada mikrovaskular dan menjadi kondisi dengan kerusakan yang berat dan berujung pada disfungsi organ. Kondisi DIC dapat diidentifikasi dengan menggunakan sistem skoring ISTH seperti pada tabel 2. Skoring tersebut meliputi penilaian risiko dan pemeriksaan laboratorium hitung trombosit, D-dimer, PT serta fibrinogen.

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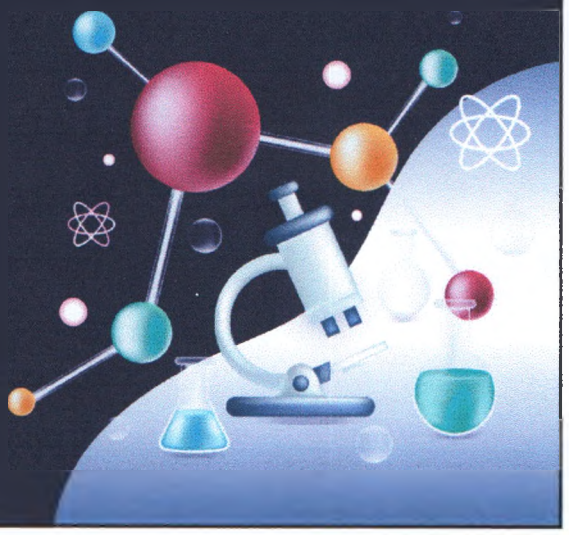
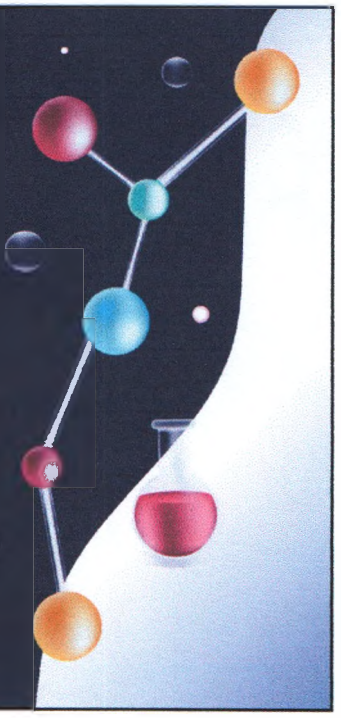
# PEMANFAATAN TES D-DIMER PADA LABORATORIUM DAN PRAKTEK KLINIS

* * * Dr.dr.Rikarni,SpPK(K) * * *

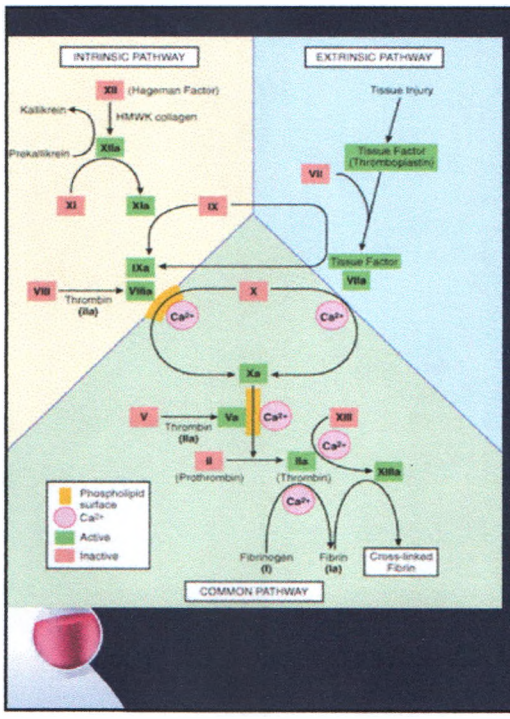


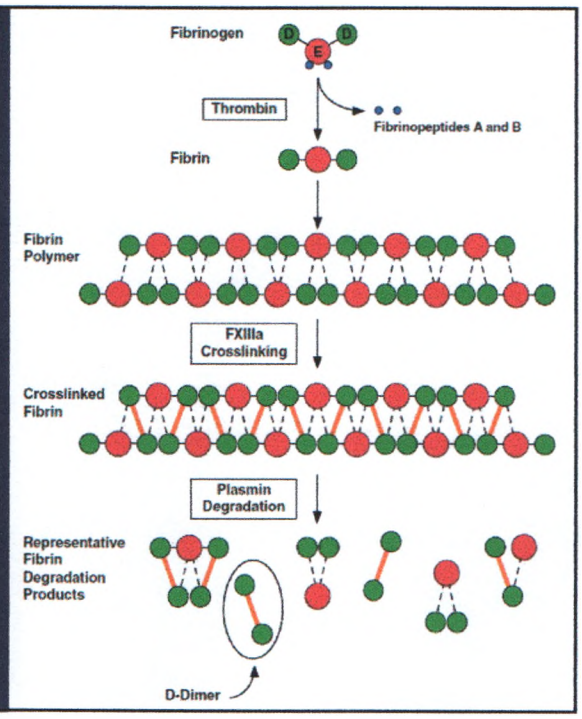
## D-Dimer

- Marker aktivasi koagulasi dan fibrinolysis
- Merupakan fibrin degradation product
- dihasilkan dari degradasi sistemik trombus vaskuler melalui mekanisme fibrinolitik
- Indikator trombosis intravaskuler



- berat molekul berkisar 190 - 10.000 kDa
- dibersihkan ginjal dan sistem retikuloendotelial
- Waktu paruh plasma D-dimer adalah 8 jam,
- Dalam kondisi fisiologis normal,
  sekitar 2-3% fibrinogen diubah menjadi fibrin,
  → D-dimer ditemukan dalam jumlah kecil pada subyek sehat
  dan cenderung meningkat seiring bertambahnya usia

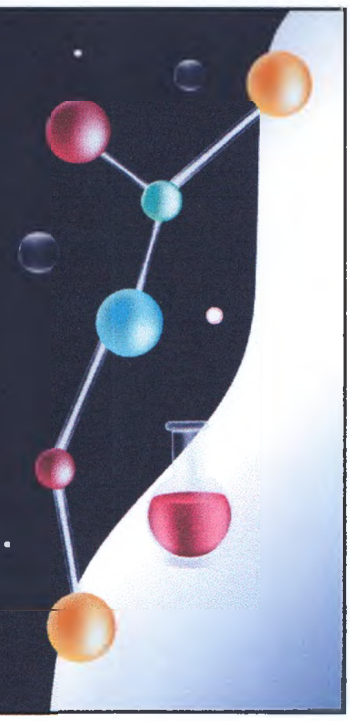


## TES D-Dimer

- Simpel, tidak invasive dan tidak mahal
- terdeteksi dalam darah lengkap, plasma, atau serum
- menggunakan antibodi monoklonal yang mengenali eptop spesifik molekul D-dimer ikatan silang

  yang tidak ada di D-domain fibrinogen dan fibrin monomer
- Tes VIDAS D-Dimer, metode yang luas digunakan dilaporkan tidak ada gangguan dari heparin, bilirubin, hemoglobin, produk degradasi fibrin, atau kekeruhan plasma



The D-dimer assay

Eric D. Johnson[1] | John C. Schell[2] | George M. Rodgers[1]

*Am J Hematol.* 2019;94:833–839.

## Tes D-Dimer

01 **Latex agglutination**

02 **Immunoturbidimetry**

03 **ELISA**
enzyme-linked immunosorbent assays

04 **ELFA**
enzyme-linked immunofluorescence assays

05 **CLIA**
Chemiluminescent enzyme immunometric assay

# Praanalitik

## 01 Pengambilan sampel

- ❑ Butterfly devices , ukuran
- ❑ Material tabung
- ❑ Antikoagulan (atau tube additive)
- ❑ Tourniquet

## 02 Pengiriman sampel

## 03 Sampling processing

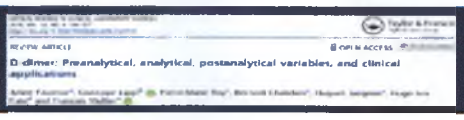
- ❑ sentrifugasi
- ❑ Substansi yang mengganggu

## 04 Stabilitas, penyimpanan dan freeze-thaw effects

Table 2. Specific pre-analytical data regarding D-dimer testing.

| Pre-analytical variables | General recommendations in hemostasis laboratories | Specific data regarding D-dimer |
|---|---|---|
| Sample collection | | |
| Needle bore size | 19–22 G | 23–25 G also tolerated |
| Butterfly devices | Discouraged | Tolerated |
| Tube material | Non-activating material (silicone-coated glass or polypropylene plastic) | Glass or plastic |
| Anticoagulant sample | Sodium citrate 3.2% (105–109 mmol/L) | Sodium citrate or heparin[a] |
| Tourniquet use | Removed as soon as the needle is in the vein (max 1–2 min) | Longer tourniquet use (i.e. 3 min) not tolerated |
| Sample delivery to the laboratory | At RT (15–22 °C), in vertical position, usually <1 h | PTS tolerated |
| Sample processing | | |
| Centrifugation | At RT, 1500 × *g* for at least 15 min | Faster protocol allowed (at RT, 4500 × *g* for 2 min) |
| Interfering substances | Do not analyze samples with hemolysis | Cell-free hemoglobin i.e. <3 g/L tolerated |
| Stability, storage and F/T effects | At RT (15–22 °C), no more than 4 h | At least 24 h at RT or at 2–8 °C or years at −60 to −80 °C<br>No impact of F/T procedure |

RT: gauge; RT: room temperature; PTS: pneumatic tube system; F/T: freezing/thawing.
[a]correction factor needed (dilution).


D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications

# Analitik

01 **Tes D-dimer**

02 **Variasi interlaboratorium**

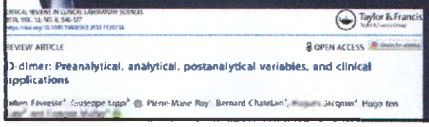
- Variability across assays
- Calibrators

03 **Standarisasi**

04 **Rekomendasi pada performance of D dimer assays**

4.

| | ELISA | ELFA | Unenhanced latex agglutination assay | CLIA | Latex-enhanced immunoturbidimetric assay | POC assay |
|---|---|---|---|---|---|---|
| Type | Quantitative | Quantitative | Qualitative/semi-quantitative | Quantitative | Quantitative | Qualitative/ quantitative |
| TAT | 2–4 h | 35–40 min | Rapid | 25–40 min | 15 min | 2–20 min |
| Pros | Considered as the gold standard, sensitivity, observer-independent | Considered as reference method, most validated method, sensitivity, automation, wider linear range, automated, observer-independent | Rapid, inexpensive | Sensitivity, rapid, automated, observer-independent | Sensitivity, automated, rapid, observer-independent | Readily available, fas higher specificity, whole blood |
| Cons | Highly manual, technical skills, time-consuming, not optimal linear range, moderate specificity | Moderate specificity | Moderate sensitivity, manual, observer dependent | Lack clinical validation, moderate specificity | Moderate specificity | Sensitivity, not all FDA cleared, observer dependent, manual |
| Examples | Asserachrome® (Stago), Enzygnost® (Dade Behring) | Vidas® (bioMérieux) | Dimertest latex® (IL), Fibrinosticon® (bioMérieux), Dade Dimertest® (Siemens) | AcuStar® (Werfen), Immulite® (Siemens) | Tina-quant® (Roche), STA-Liatest® (Stago), HemosIL HS® (Werfen) Innovance® (Dade Behring) | SimpliRed® (Agen), Clearview Simplify® (Agen) |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REVIEW ARTICLE

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D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications

**Table 1.** Characteristics of common D-dimer assays. Relevant central laboratory and point-of-care assays are shown along with the manufacturer, method design, method principle, unit type, cut-off mentioned by the manufacturer, and the intended use issued by the FDA regarding PE. DDU, D-dimer units; FDA, U.S. Food and Drugs Administration; FEU, fibrinogen-equivalent units; NA, not applicable; PE, pulmonary embolism; POC, point-of-care.

| Assay Type | Assay Name | Manufacturer | Design | Principle | Unit Type | Manufacturer's Cut-Off | FDA Intended Use (PE) |
|---|---|---|---|---|---|---|---|
| Central lab | Advanced D-Dimer | Siemens Healthcare Diagnostics (previously Dade Behring) | Quantitative | Latex-enhanced turbidimetric immunoassay | FEU | BCS System 1 0.5 mg/l Siemens CA-1500 1.0 mg/l | Aid in diagnosis |
| Central lab | AxSYM D-Dimer | Abbott laboratories | Quantitative | Enzyme-linked fluorescent assay | FEU | 500 µg/L | NA |
| Central lab | Diagnostica D-Dimer | Diagnostica Laboratorium | Quantitative | Latex-enhanced turbulent [illegible] | FEU | 0.5 µg/mL | Aid in diagnosis |
| Central lab | Hemosil AcuStar D-Dimer | Werfen (previously Instrumentation Laboratory) | Quantitative | Chemiluminescent immunoassay | FEU | 500 µg/l | Aid in diagnosis |
| Central lab | Hemosil D-Dimer (±HS) | Werfen (previously Instrumentation Laboratory) | Quantitative | Latex-enhanced turbidimetric immunoassay | DDU | 230 µg/L | Exclusion |
| Central lab | Hemosil D-Dimer HS 500 | Werfen (previously Instrumentation Laboratory) | Quantitative | Latex-enhanced turbidimetric immunoassay | FEU | 500 µg/l | Exclusion |
| Central lab | INNOVANCE D-Dimer | Siemens Healthcare Diagnostics | Quantitative | Latex-enhanced turbidimetric immunoassay | FEU | 0.5 mg/L | Exclusion |
| Central lab | STA Liatest D-DI | Diagnostica Stago | Quantitative | Latex-enhanced turbidimetric immunoassay | FEU | 0.5 µg/mL | Exclusion |
| Central lab | Tina-Quant D-Dimer | Roche Diagnostics | Quantitative | Latex-enhanced turbidimetric immunoassay | FEU | 0.5 µg/mL | Exclusion |
| Central lab (or POC) | VIDAS D-Dimer | bioMerieux | Quantitative | Enzyme-linked fluorescent assay | FEU | 500 µg/l | Exclusion |
| POC | AQT90 FLEX D-dimer | Radiometer Medical ApS | Quantitative | Time-resolved fluorometry | NA | 500 µg/l | NA |
| POC | Clearview hemosIL | Ager Biomedical | Qualitative | Solid-phase immunochromatography | Neg/pos | 80 µg/l | NA |
| POC | INNOVANCE D-Dimer | Mitsubishi Kagaku Iatron | Quantitative | Chemiluminescent immunoassay | FEU | 0.686 µg/mL | NA |
| POC | Roche Cardiac D-dimer | Roche Diagnostics | Quantitative | Solid-phase immunochromatography | FEU | 0.5 µg/mL | NA |
| [illegible] | Stratus CS | [illegible] | [illegible] | Fluorescent | [illegible] | [illegible] | [illegible] |

Review

**D-dimer Testing in Pulmonary Embolism with a Focus on Potential Pitfalls: A Narrative Review**

Loris Wauthier [1,*], Julien Favresse [1,2,*], Michael Hardy [3], Jonathan Douxfils [4,5], Grégoire Le Gal [6], Pierre-Marie Roy [7], Nick van Es [8,9], Cihan Ay [10], Hugo ten Cate [11,12], Thierry Vander Borght [13,14,15], Michaël V. Dupont [16], Thomas Lecompte [1,17], Giuseppe Lippi [18] and François Mullier [1,19,*]

*Diagnostics* 2022, *12*, 2770. https://doi.org/10.3390/diagnostics12112770


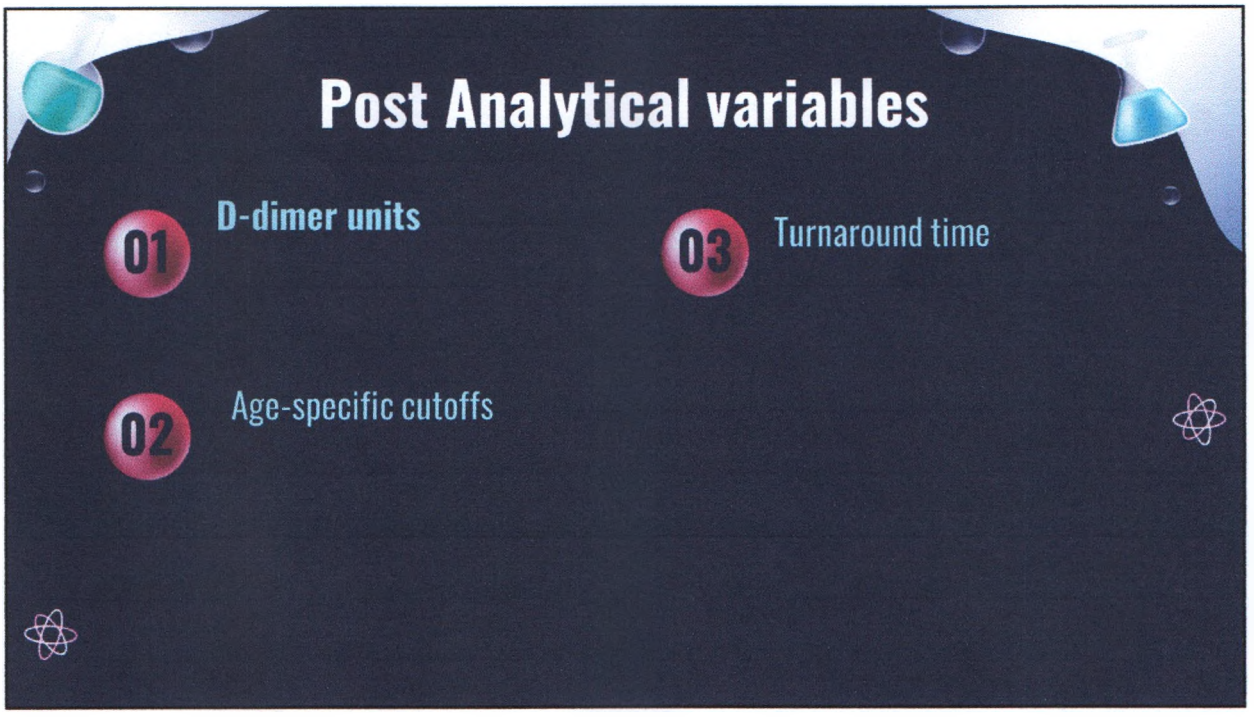

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**TABLE 1** Comparison of categories of D-dimer assays

| | ELISA | ELFA | Latex-enhanced immunoturbidimetric | Whole-blood point of care |
|---|---|---|---|---|
| Description | Quantitative | Quantitative | Quantitative | Qualitative |
| Turnaround time | 2-4 h | 35 min | 15 min | 2-5 min |
| Sensitivity[a] (95% CI) | 94% (86-97) | 96% (89-98) | 93% (89-95) | 83% (67-93) |
| Specificity[a] (95% CI) | 53% (38-68) | 46% (31-61) | 53% (46-61) | 71% (57-82) |
| Advantages | High sensitivity | High sensitivity<br>Fully automated | Comparable sensitivity to ELISA<br>Fully automated | Can be performed at bedside<br>Higher specificity |
| Disadvantages | Labor-intensive<br>Moderate specificity | Moderate specificity | Moderate specificity | Observer dependent<br>Lower sensitivity |

ELISA, enzyme-linked immunosorbent assay; ELFA, enzyme-linked immunofluorescence assay.
[a]Summary estimates for diagnosis of DVT reported in systematic review by Di Nisio et al.[11]

Review of D-dimer testing: Good, Bad, and Ugly

L.-A. Linkins[1,2] | S. Takach Lapner[1,2]

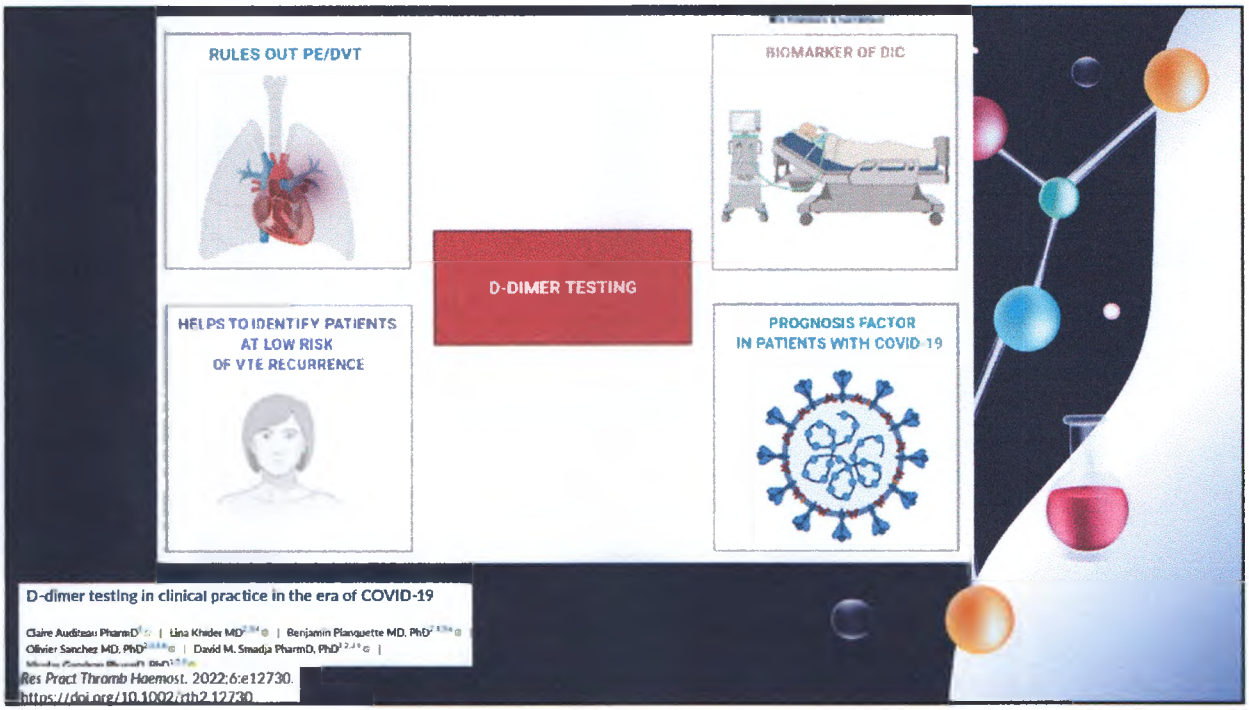
*Int J Lab Hem.* 2017;39(Suppl. 1):98-103.

## Pemanfatan D- Dimer untuk VTE

- menyingkirkan diagnosis vena tromboemboli (VTE) pada pasien dengan *low clinical probability* sesuai skor prediksi klinis

  DVT dan PE

- Menetapkan risiko trombosis berulang untuk menentukan durasi optimal antikoagulan pada VTE



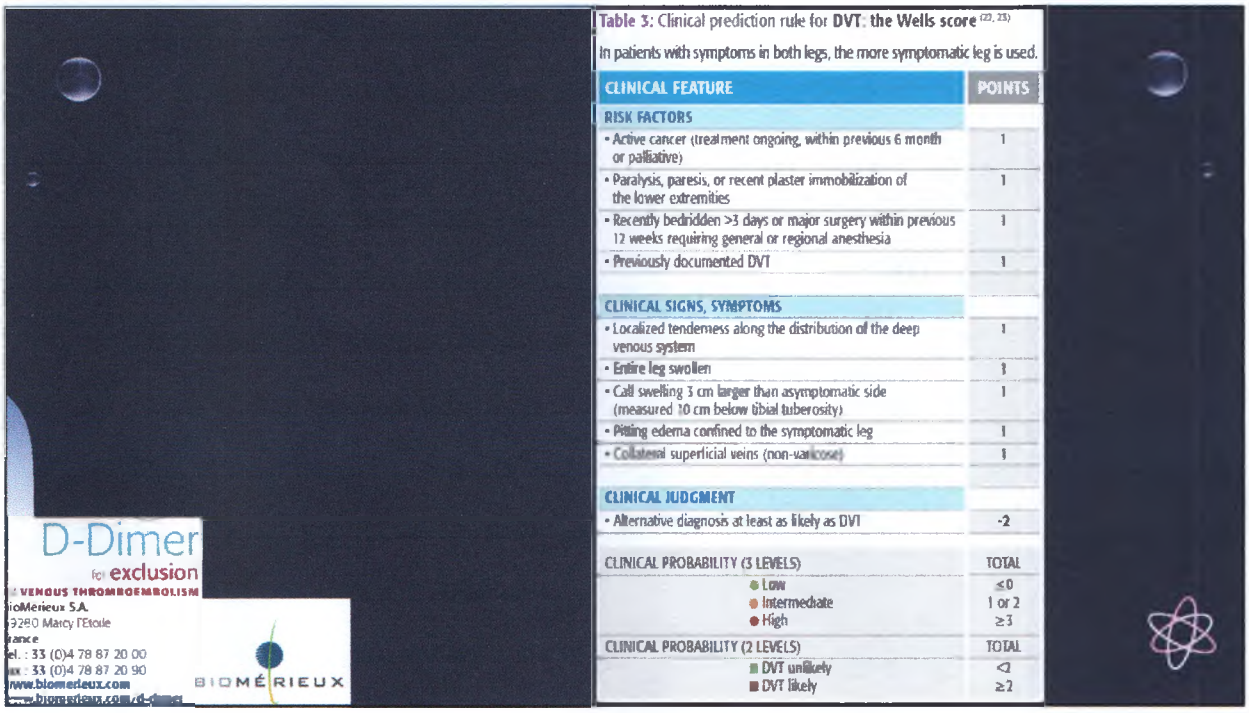




**Table 3:** Clinical prediction rule for **DVT: the Wells score** [22, 23]

In patients with symptoms in both legs, the more symptomatic leg is used.

| CLINICAL FEATURE | POINTS |
|---|---|
| **RISK FACTORS** | |
| • Active cancer (treatment ongoing, within previous 6 month or palliative) | 1 |
| • Paralysis, paresis, or recent plaster immobilization of the lower extremities | 1 |
| • Recently bedridden >3 days or major surgery within previous 12 weeks requiring general or regional anesthesia | 1 |
| • Previously documented DVT | 1 |
| **CLINICAL SIGNS, SYMPTOMS** | |
| • Localized tenderness along the distribution of the deep venous system | 1 |
| • Entire leg swollen | 1 |
| • Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity) | 1 |
| • Pitting edema confined to the symptomatic leg | 1 |
| • Collateral superficial veins (non-varicose) | 1 |
| **CLINICAL JUDGMENT** | |
| • Alternative diagnosis at least as likely as DVT | -2 |
| CLINICAL PROBABILITY (3 LEVELS) | TOTAL |
| ● Low | ≤0 |
| ● Intermediate | 1 or 2 |
| ● High | ≥3 |
| CLINICAL PROBABILITY (2 LEVELS) | TOTAL |
| ■ DVT unlikely | <2 |
| ■ DVT likely | ≥2 |

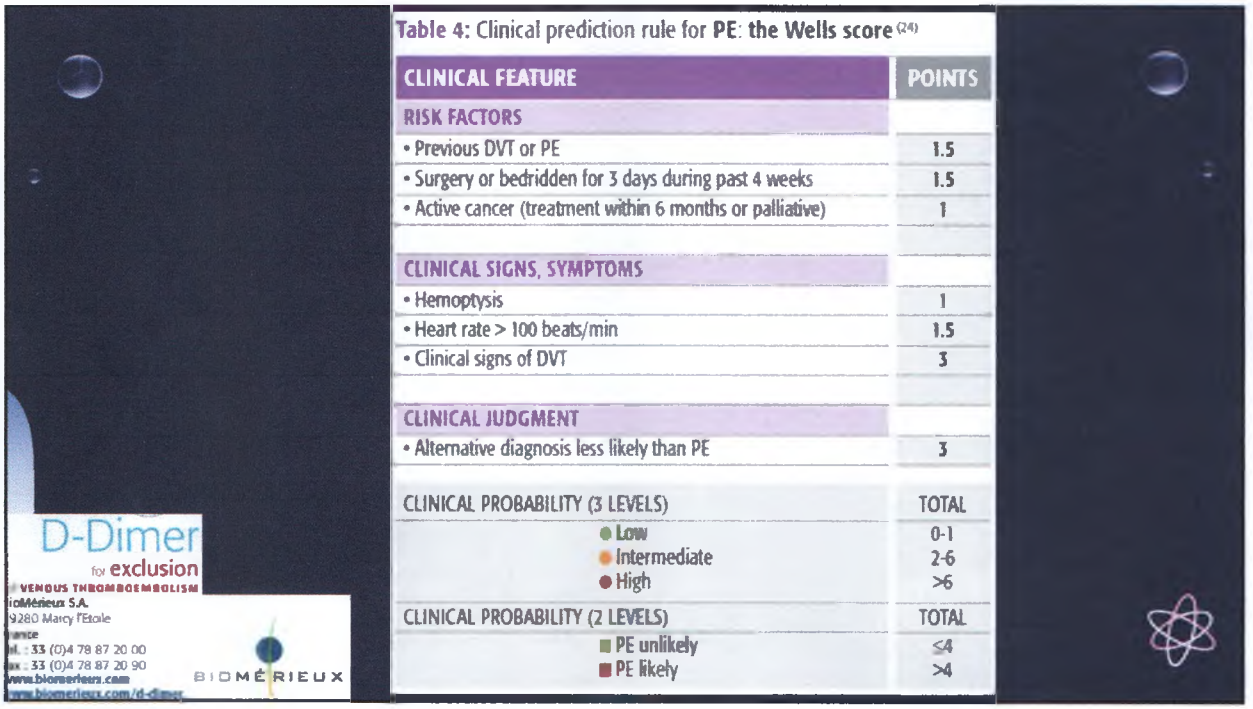



**Table 4:** Clinical prediction rule for **PE**: **the Wells score** [24]

| CLINICAL FEATURE | POINTS |
|---|---|
| **RISK FACTORS** | |
| • Previous DVT or PE | 1.5 |
| • Surgery or bedridden for 3 days during past 4 weeks | 1.5 |
| • Active cancer (treatment within 6 months or palliative) | 1 |
| **CLINICAL SIGNS, SYMPTOMS** | |
| • Hemoptysis | 1 |
| • Heart rate > 100 beats/min | 1.5 |
| • Clinical signs of DVT | 3 |
| **CLINICAL JUDGMENT** | |
| • Alternative diagnosis less likely than PE | 3 |
| CLINICAL PROBABILITY (3 LEVELS) | TOTAL |
| ● Low | 0-1 |
| ● Intermediate | 2-6 |
| ● High | >6 |
| CLINICAL PROBABILITY (2 LEVELS) | TOTAL |
| ■ PE unlikely | ≤4 |
| ■ PE likely | >4 |

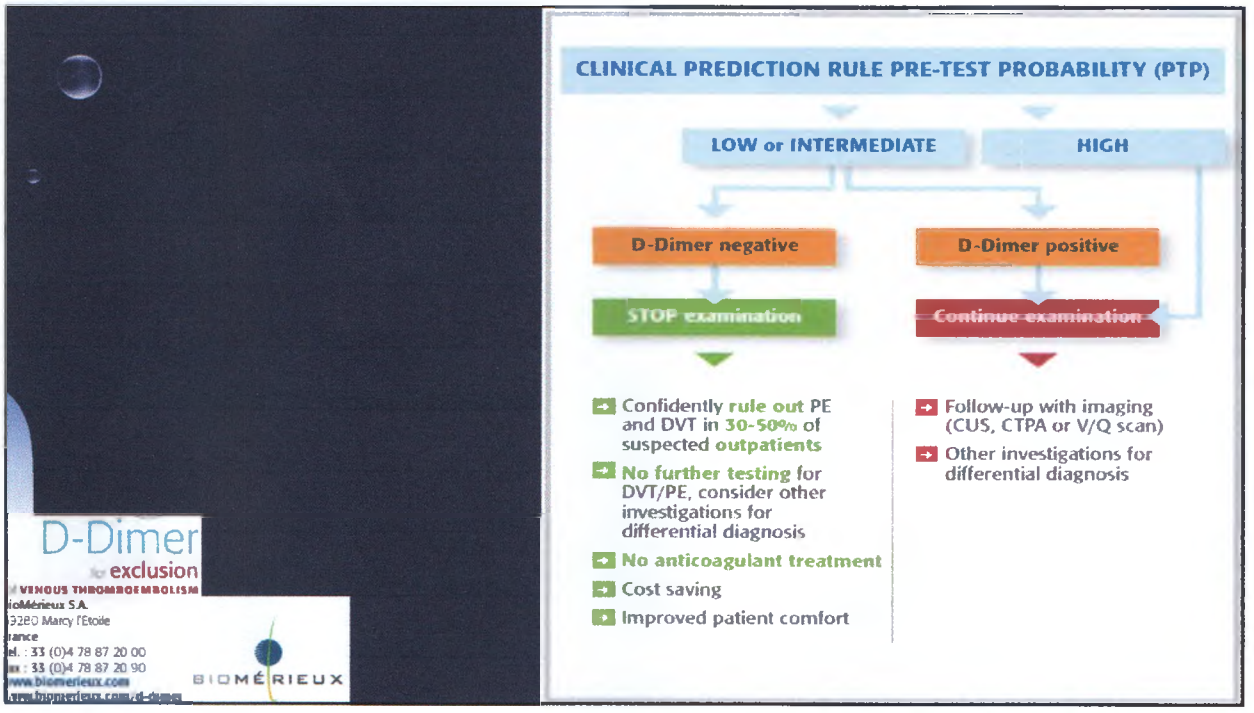


**TABLE 1** Central laboratory D-dimer assays frequently used in VTE clinical trials

| Assay | Manufacturer's cutoff for detection[a] | DVT sensitivity | DVT specificity |
|---|---|---|---|
| Asserachrom D-dimer | 500 ng/mL FEU | 98% (91-100%) | 47% (29-65%) |
| Clearview Simplify D-dimer | 500 ng/mL DDU | 100% (92-100%) | 48% (43-53%) |
| Hemosil D-dimer HS 500 | 500 ng/mL DDU | 100% (85-99%) | 45% (41-49%) |
| Innovance D-dimer | 500 ng/mL FEU | 99% (97-99%) | 40% (38-40%) |
| MiniQuant D-dimer | 200 ng/mL DDU | 96% (95-98%) | 44% (40-47%) |
| STA-Liatest D-dimer | 500 ng/mL FEU | 96% (90-100%) | 47% (33-76%) |
| TinaQuant D-dimer | 500 ng/mL FEU | 99% (90-100%) | 46% (39-72%) |
| Vidas D-dimer | 500 ng/mL FEU | 100% (82-100%) | 42% (37-46%) |
| **Assays** | **Manufacturer's cutoff for detection[a]** | **DVT sensitivity** | **DVT specificity** |
| LABGEO | 450 ng/mL FEU | 99% (93-100%) | 53% (38-68%) |
| Roche Cardiac D-dimer | 500 ng/mL FEU | 95% (88-99%) | 62% (58-67%) |
| PATHFAST D-dimer | 570 ng/mL FEU | 98% (94-100%) | 40% (35-44%) |
| SimpliRED D-dimer | 400 ng/mL FEU | 94% (84-95%) | 67% (56-84%) |
| TRIAGE | 200 ng/mL DDU | 97% (93-100%) | 48% (44-53%) |

Abbreviations: DDU, D-dimer units; DVT, deep vein thrombosis; FEU, fibrinogen equivalent units.
[a]Values as per Manufacturer Package Insert, FDA Memorandum, and Independent expert comparison. References: 5,26–37. Other studies might report other sensitivities/specificities. Reported ranges represent 95% CI.

The D-dimer assay

Eric D. Johnson[1] | John C. Schell[2] | George M. Rodgers[1]

Am J Hematol. 2019;94:833–839

## PEMANFAATAN TES D-DIMER PADA DIC

- Pengujian D-dimer sangat berguna dalam mengevaluasi pasien dengan kemungkinan DIC,
- pasien dengan koagulopati yang tidak diketahui
- DIC mengidentifikasi tingkat D-dimer yang konsisten dengan diagnosis
- dari DIC.
- Rekomendasi ISTH DIC scoring system

# D I C (disseminated intravascular coagulation

suatu sindrom didapat yang ditandai dengan aktivasi koagulasi intravascular yang luas yang timbul dari beragam penyebab .

→ gangguan yang mendasarinya,

→ Aktivasi koagulasi dan fibrinolisis

→ Konsumsi trombosit dan faktor koagulasi

Diagnosis DIC harus mencakup klinis dan laboratorium

Sistem penilaian DIC dari International Society for Thrombosis dan Haemostasis (ISTH) memberikan pengukuran objektif DIC.

# Kelainan dasar yang sering menyebabkan DIC

- Sepsis : bakteri ( staphylococcus,streptococcus, pneumococcus, meningococcus, batang gram negatif), virus, jamur, parasite, rickettsia
- Trauma dan cedera jaringan : cedera otak, luka bakar yang luas, emboli lemak, rhabdomiolisis
- Kelainan vaskuler : giant hemangioma, emboli amnion, sindrom kematian janin, abortus sepsis
- Kanker : adenokarsinoma ( prostat, pancreas), keganasan hematologi ( leukemia promielositik akut)
- Kelainan imunologi : reaksi transfuse hemolitik akut, organ or tissue transplant rejection, graft-versus-host disease
- Obat : agen fibrinolitik, warfarin, reaksi obat ( amfetamin)
- Bisa ular
- Penyakit hepar : Fulminant hepatic failure, sirosis hati

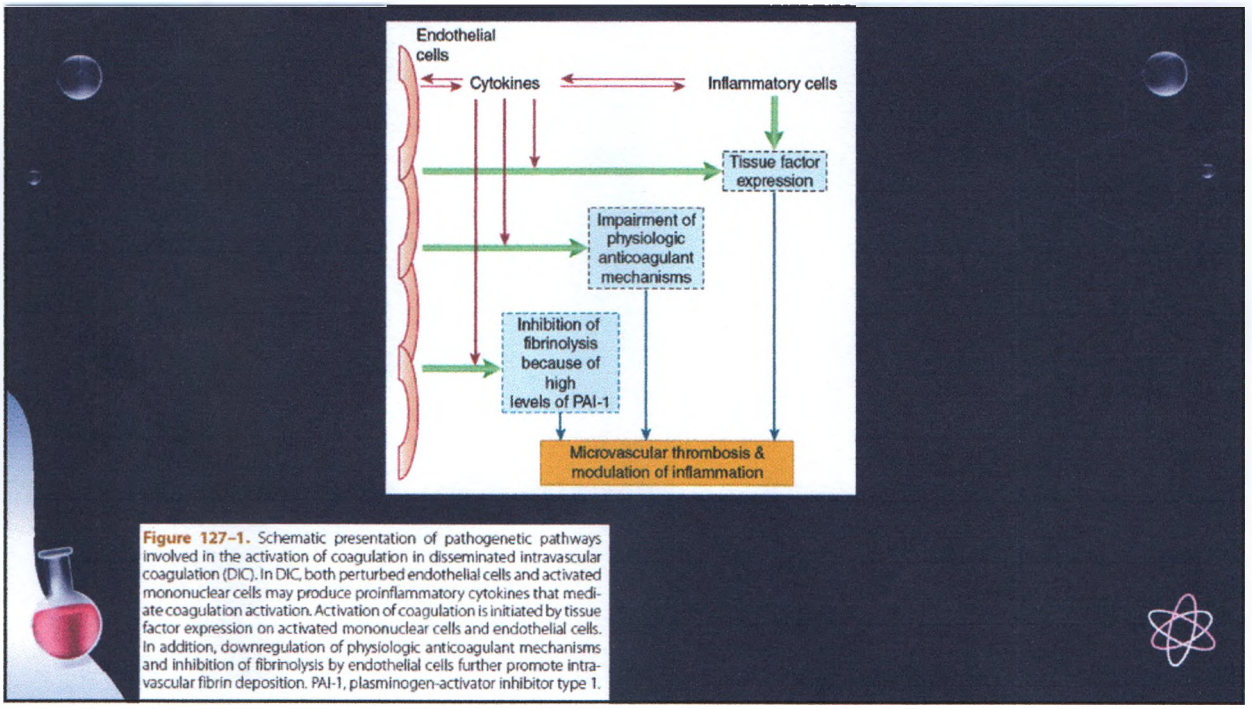



**Figure 127–1.** Schematic presentation of pathogenetic pathways involved in the activation of coagulation in disseminated intravascular coagulation (DIC). In DIC, both perturbed endothelial cells and activated mononuclear cells may produce proinflammatory cytokines that mediate coagulation activation. Activation of coagulation is initiated by tissue factor expression on activated mononuclear cells and endothelial cells. In addition, downregulation of physiologic anticoagulant mechanisms and inhibition of fibrinolysis by endothelial cells further promote intravascular fibrin deposition. PAI-1, plasminogen-activator inhibitor type 1.

Penilaian risiko

- ❑ Apakah pasien mempunyai kelainan dasar yang diketahui berhubungan dengan dic
- ❑ Jika ya lanjutkan algoritma ;
- ❑ Lakukan pemeriksaanhitung trombosit, D-Dimer, PT, Fibrinogen

- ❑ Hitung skor sbb ;
- ❑ > atau sama dengan 5 sesuai ov

**TABLE 4** ISTH DIC scoring system[a]

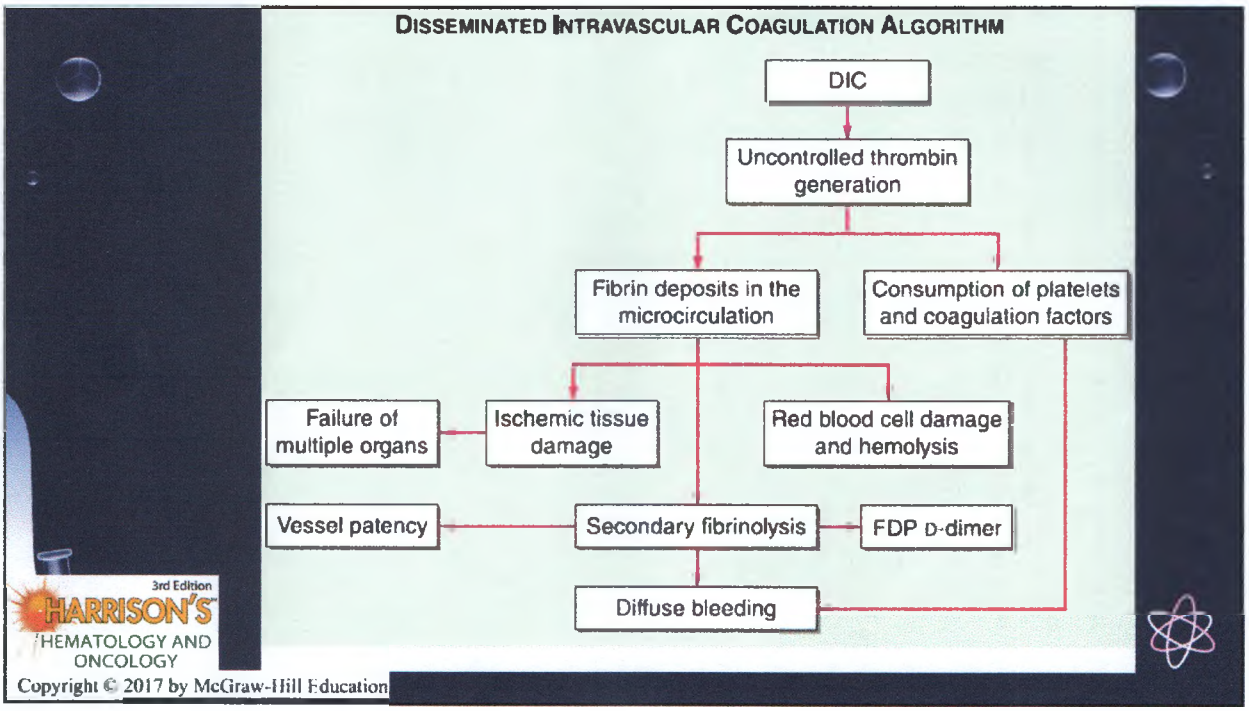
| Test | Score |
|---|---|
| Platelet count | >100 000 = 0 |
| | 50 000-100 000 = 1 |
| | <50 000 = 2 |
| D-Dimer | No increase = 0 |
| | Moderate increase = 1 |
| | Strong increase = 2 |
| Prolongation of PT | <3 s = 0 |
| | >3 but < 6 s = 1 |
| | >6 s = 2 |
| Fibrinogen mg/dL | >100 mg/dL = 0 |
| | <100 mg/dL = 1 |
| | Score ≥5 = overt DIC |

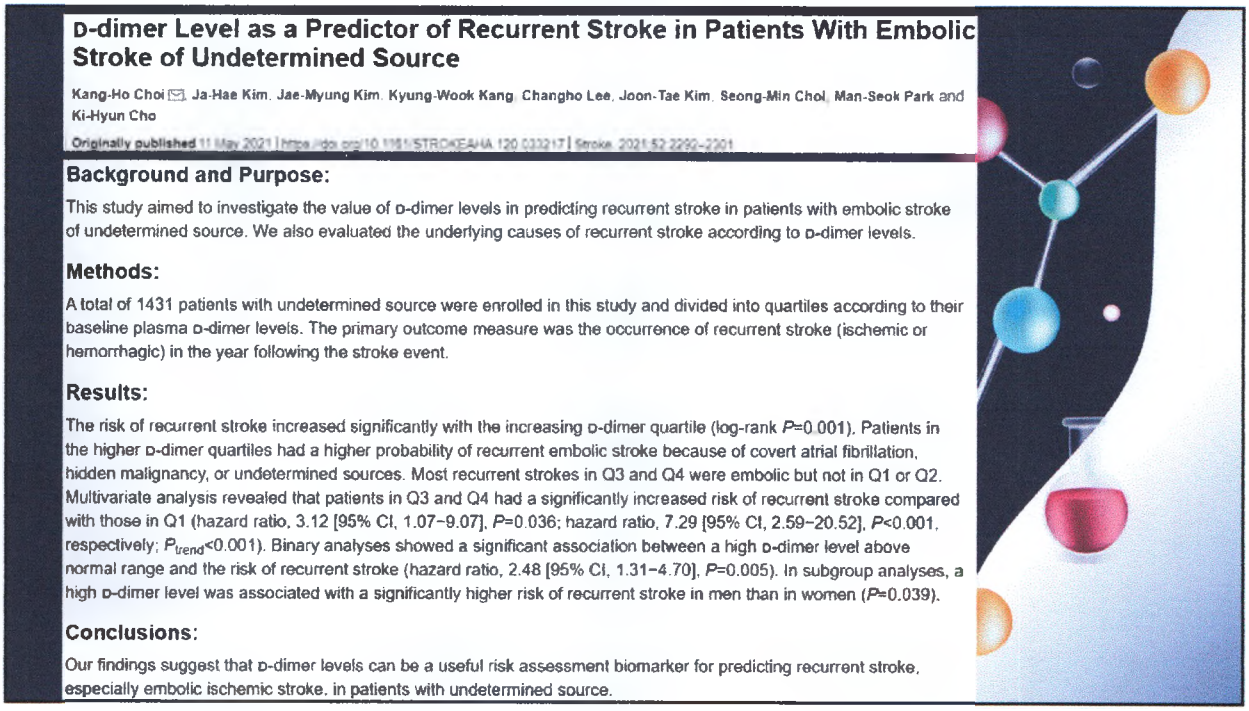
Abbreviations: DIC, disseminated intravascular coagulation; ISTH, International Society of Thrombosis and Haemostasis; PT, prothrombin time.

The D-dimer assay

Eric D. Johnson | John C. Schell | George M. Rodgers

*Am J Hematol.* 2019;94:833–839.



## D-dimer Level as a Predictor of Recurrent Stroke in Patients With Embolic Stroke of Undetermined Source

Kang-Ho Choi ✉, Ja-Hae Kim, Jae-Myung Kim, Kyung-Wook Kang, Changho Lee, Joon-Tae Kim, Seong-Min Choi, Man-Seok Park and Ki-Hyun Cho

Originally published 11 May 2021 | https://doi.org/10.1161/STROKEAHA.120.033217 | Stroke. 2021;52:2292–2301

### Background and Purpose:

This study aimed to investigate the value of D-dimer levels in predicting recurrent stroke in patients with embolic stroke of undetermined source. We also evaluated the underlying causes of recurrent stroke according to D-dimer levels.

### Methods:

A total of 1431 patients with undetermined source were enrolled in this study and divided into quartiles according to their baseline plasma D-dimer levels. The primary outcome measure was the occurrence of recurrent stroke (ischemic or hemorrhagic) in the year following the stroke event.

### Results:

The risk of recurrent stroke increased significantly with the increasing D-dimer quartile (log-rank $P$=0.001). Patients in the higher D-dimer quartiles had a higher probability of recurrent embolic stroke because of covert atrial fibrillation, hidden malignancy, or undetermined sources. Most recurrent strokes in Q3 and Q4 were embolic but not in Q1 or Q2. Multivariate analysis revealed that patients in Q3 and Q4 had a significantly increased risk of recurrent stroke compared with those in Q1 (hazard ratio, 3.12 [95% CI, 1.07–9.07], $P$=0.036; hazard ratio, 7.29 [95% CI, 2.59–20.52], $P$<0.001, respectively; $P_{trend}$<0.001). Binary analyses showed a significant association between a high D-dimer level above normal range and the risk of recurrent stroke (hazard ratio, 2.48 [95% CI, 1.31–4.70], $P$=0.005). In subgroup analyses, a high D-dimer level was associated with a significantly higher risk of recurrent stroke in men than in women ($P$=0.039).

### Conclusions:

Our findings suggest that D-dimer levels can be a useful risk assessment biomarker for predicting recurrent stroke, especially embolic ischemic stroke, in patients with undetermined source.

Journal of *Clinical Medicine*

MDPI

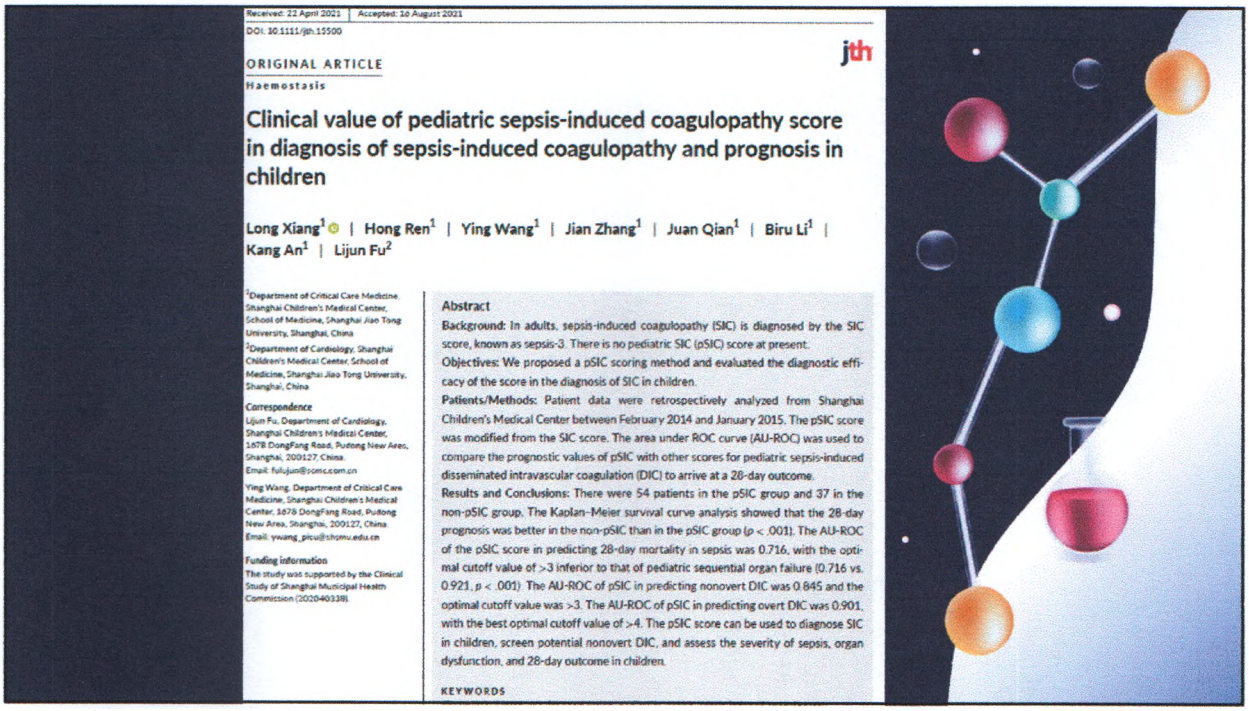
*Article*

## Baseline D-Dimer Levels as a Risk Assessment Biomarker for Recurrent Stroke in Patients with Combined Atrial Fibrillation and Atherosclerosis

**Abstract:** Background: We investigated the effect of D-dimer levels and efficacy of different antithrombotic therapies according to the baseline D-dimer levels on recurrent stroke in patients with atrial fibrillation (AF)-related stroke and atherosclerosis. Methods: We enrolled 1441 patients with AF-related stroke and atherosclerosis in this nationwide multicenter study. The primary outcome measure was the occurrence of recurrent ischemic stroke over a 3-year period. Results: High D-dimer levels (≥2 μg/mL) were significantly associated with higher risk of recurrent ischemic stroke (adjusted hazard ratio (HR), 1.80; 95% confidence interval (CI), 1.13–2.84; $p = 0.012$). The risk of recurrent stroke was similar between the anticoagulant and the antiplatelet groups in all subjects (adjusted HR, 0.78; 95% CI, 0.46–1.32; $p = 0.369$). However, in patients with high D-dimer levels (≥2 μg/mL), risk of recurrent stroke was significantly lower in the anticoagulant group than in the antiplatelet group (adjusted HR, 0.40; 95% CI, 0.18–0.87; $p = 0.022$). Conclusion: Our findings suggested that baseline D-dimer levels could be used as a risk assessment biomarker of recurrent stroke in patients with AF-related stroke and atherosclerosis. High D-dimer levels would facilitate the identification of patients who are more likely to benefit from anticoagulants to ensure secondary prevention of stroke.

**Keywords:** atrial fibrillation; d-dimer; outcome; ischemic stroke; antithrombotics

*J. Clin. Med.* **2019**, *8*, 1457; doi:10.3390/jcm8091457



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DOI: 10.1111/jth.15500

ORIGINAL ARTICLE

Haemostasis

jth

## Clinical value of pediatric sepsis-induced coagulopathy score in diagnosis of sepsis-induced coagulopathy and prognosis in children

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**Funding information**

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**Abstract**

**Background:** In adults, sepsis-induced coagulopathy (SIC) is diagnosed by the SIC score, known as sepsis-3. There is no pediatric SIC (pSIC) score at present.

**Objectives:** We proposed a pSIC scoring method and evaluated the diagnostic efficacy of the score in the diagnosis of SIC in children.

**Patients/Methods:** Patient data were retrospectively analyzed from Shanghai Children's Medical Center between February 2014 and January 2015. The pSIC score was modified from the SIC score. The area under ROC curve (AU-ROC) was used to compare the prognostic values of pSIC with other scores for pediatric sepsis-induced disseminated intravascular coagulation (DIC) to arrive at a 28-day outcome.

**Results and Conclusions:** There were 54 patients in the pSIC group and 37 in the non-pSIC group. The Kaplan–Meier survival curve analysis showed that the 28-day prognosis was better in the non-pSIC than in the pSIC group ($p < .001$). The AU-ROC of the pSIC score in predicting 28-day mortality in sepsis was 0.716, with the optimal cutoff value of >3 inferior to that of pediatric sequential organ failure (0.716 vs. 0.921, $p < .001$). The AU-ROC of pSIC in predicting nonovert DIC was 0.845 and the optimal cutoff value was >3. The AU-ROC of pSIC in predicting overt DIC was 0.901, with the best optimal cutoff value of >4. The pSIC score can be used to diagnose SIC in children, screen potential nonovert DIC, and assess the severity of sepsis, organ dysfunction, and 28-day outcome in children.

KEYWORDS

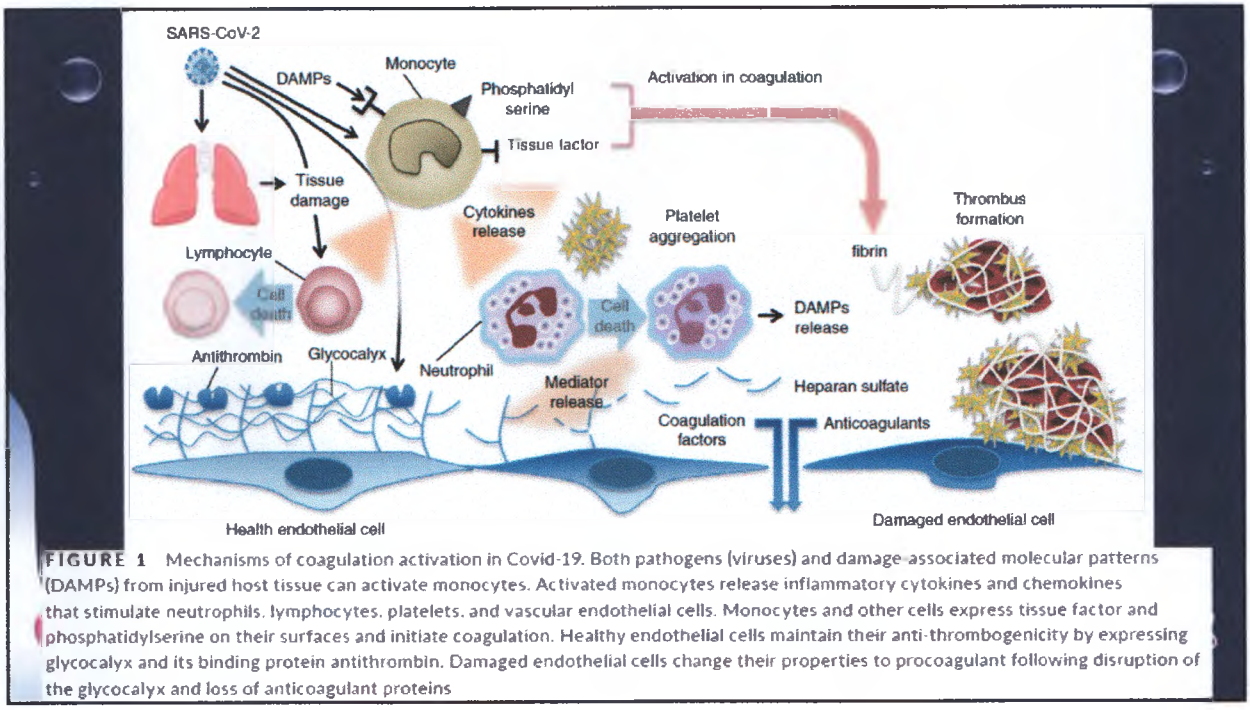



**FIGURE 1** Mechanisms of coagulation activation in Covid-19. Both pathogens (viruses) and damage-associated molecular patterns (DAMPs) from injured host tissue can activate monocytes. Activated monocytes release inflammatory cytokines and chemokines that stimulate neutrophils, lymphocytes, platelets, and vascular endothelial cells. Monocytes and other cells express tissue factor and phosphatidylserine on their surfaces and initiate coagulation. Healthy endothelial cells maintain their anti-thrombogenicity by expressing glycocalyx and its binding protein antithrombin. Damaged endothelial cells change their properties to procoagulant following disruption of the glycocalyx and loss of anticoagulant proteins

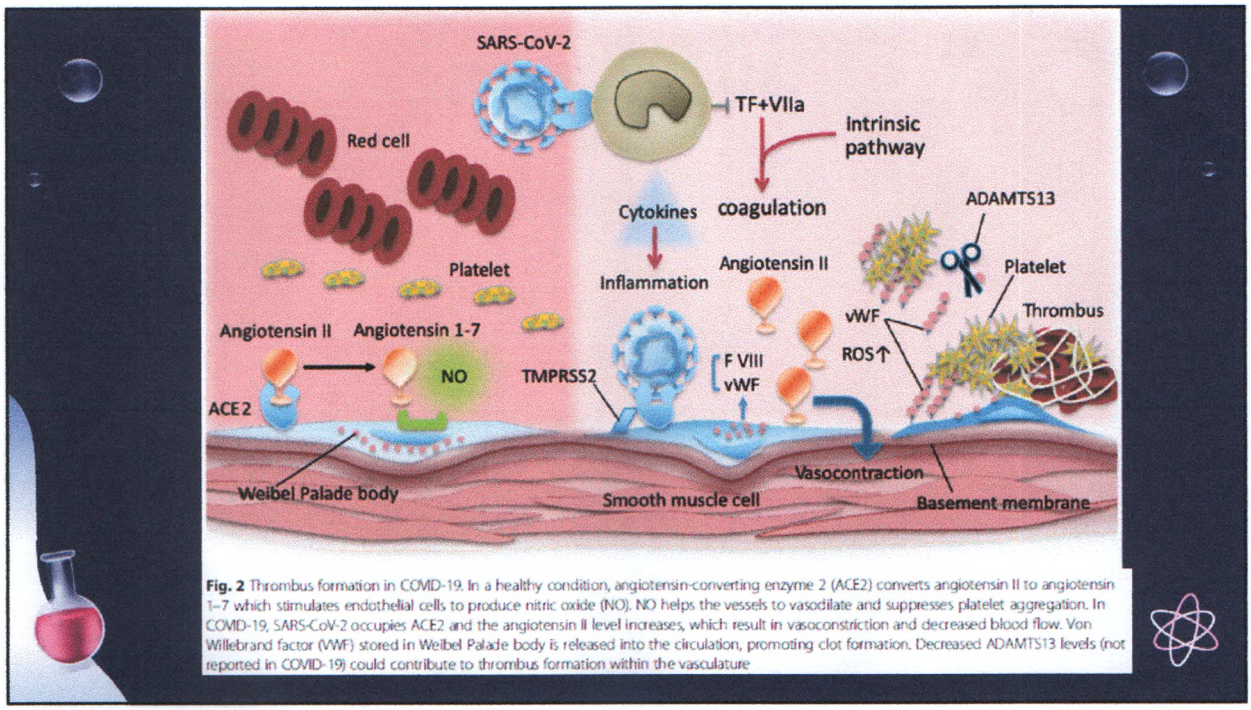



**Fig. 2** Thrombus formation in COVID-19. In a healthy condition, angiotensin-converting enzyme 2 (ACE2) converts angiotensin II to angiotensin 1–7 which stimulates endothelial cells to produce nitric oxide (NO). NO helps the vessels to vasodilate and suppresses platelet aggregation. In COVID-19, SARS-CoV-2 occupies ACE2 and the angiotensin II level increases, which result in vasoconstriction and decreased blood flow. Von Willebrand factor (VWF) stored in Weibel Palade body is released into the circulation, promoting clot formation. Decreased ADAMTS13 levels (not reported in COVID-19) could contribute to thrombus formation within the vasculature

**Recommendations for Minimal Laboratory Testing Panels in Patients with COVID-19: Potential for Prognostic Monitoring**

Emmanuel J. Favaloro, PhD, FFSc (RCPA)[1] Giuseppe Lippi, MD[2]

Semin Thromb Hemost 2020;46:379–382.

**Table 1** Recommendations for laboratory tests in patients with COVID-19[a]

| Test | Abbreviation | Rationale for inclusion | Considerations |
|---|---|---|---|
| Hematology (including hemostasis/coagulation) | | | |
| Complete/full blood count | CBC/FBC | Identification of lymphopenia, neutrophilia, and thrombocytopenia | Include platelet count, differential for lymphocyte count |
| Prothrombin Time | PT | Identification of ongoing coagulopathy | |
| Activated partial thromboplastin time | APTT | | |
| Fibrinogen | Fbg or Fib | Identification of ongoing (consumption) coagulopathy | |
| D-dimer | | Identification of ongoing (consumption or thrombotic) coagulopathy | [b] |
| Biochemistry and other tests | | | |
| Electrolytes | | Identification of metabolic derangement | |
| Glucose | | | |
| Creactive protein | CRP | Monitoring of infection/inflammatory response | [b] |
| Lactate dehydrogenase | LDH | Identification of lung injury and/or multiple organ failure | |
| Aspartate aminotransferase | AST | Identification of liver injury | |
| Alanine aminotransferase | ALT | | |
| Bilirubin | | | |
| Albumin | | Identification of liver failure | |
| Creatine kinase (also known as creatine phosphokinase or phosphocreatine kinase) | CK | Identification of muscle injury | |
| Lipase | | Identification of pancreatic injury | |
| Blood urea nitrogen | BUN | Identification of kidney injury and/or failure | |
| Creatinine | | | |
| Cardiac biomarkers (troponin I or T) | | Identification of cardiac injury | [b] |
| Brain natriuretic peptide | BNP | Identification of cardiac failure | [c] |
| Ferritin | | Monitoring of infection/inflammatory response | [b] |
| Procalcitonin | PCT | Identification of bacterial coinfections | [c] |
| Presepsin | | Monitoring of severity of viral infection | [d] |

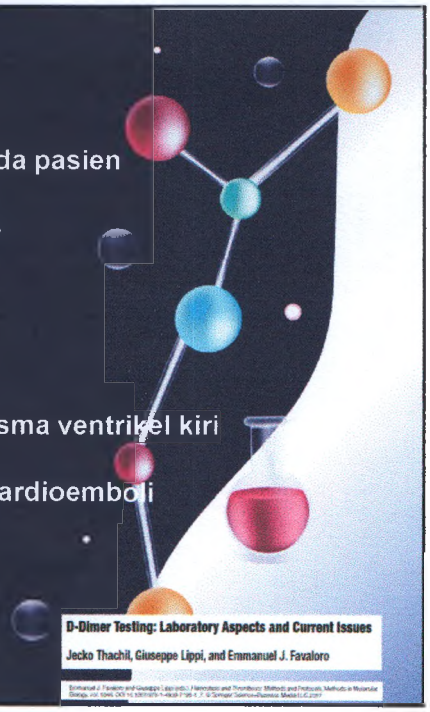
Abbreviation: COVID-19, coronavirus disease 2019.
[a] Parameters may have some prognostic value in COVID-19 patients. However, we recognize that such a list is by no means all-inclusive and patients may have limits and may quickly change as new information emerges. Thus, at all times, local experts should be consulted as available and testing modified accordingly.
[b] "Rating rule": unless clinically justified, testing should not generally be considered within 24 hours of an existing test.
[c] For selected patients with signs of MOF/SIRS, discuss with an expert (laboratory) clinician/consultant clinical scientist.

## KESIMPULAN

Pemanfaatan D-Dimer secara luas untuk

- menyingkirkan diagnosis vena tromboemboli (VTE) pada pasien dengan *low clinical probability* sesuai skor prediksi klinis DVT dan PE
- Menetapkan risiko trombosis berulang untuk menentukan durasi optimal antikoagulan pada VTE
- mendiagnosis dan memantau koagulasi intravaskular diseminata,
- memonitor kondisi pada pasien berisiko tinggi mengalami perdarahan atau trombosis.

- menyingkirkan diagnosis diseksi aorta akut
- Memprediksi dan memantau komplikasi trombotik pada pasien dengan infeksi berat (oleh bakteri , virus) dan sepsis
- Deteksi risiko trombotik pada keganasan,
- Krisis vaso-oklusif pada penyakit sel sabit
- Kecurigaan adanya trombus intrakradiak pada aneurisma ventrikel kiri
- Memprediksi stroke berulang pada penderita stroke kardioemboli
- Prognostik pada penyakit arteri perifer




# TERIMAKASIH